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Positional candidate genes for residual intake and gain in Nelore beef cattle

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ABSTRACT: Feed efficiency is jointly determined by productivity and feed requirements, both of which are economically relevant traits in beef cattle production systems. The objective of this study was to identify genes/QTLs associated with residual intake and gain (RIG) in Nelore cattle using Illumina BovineHD BeadChip (770k SNP) genotypes from 593 Nelore steers. The Bayes B analysis was completed with Gensel software parameterized to fit fewer markers than animals. Genomic windows containing all the SNP loci in each 1 Mb that accounted for more than 0.5% of genetic variance were considered as QTL. Candidate genes within windows were annotated by putative function based on DAVID and Gene Ontology. One genomic region, on BTA18, explained >0.5% of genetic variance for RIG. Three candidates genes are annotated in this region; *PHKB*, *VPS35* and *DNAJA2*. This region was associated with other feed efficiency traits, feed conversion ratio and feed efficiency. The positional candidate genes reported in this study were never reported before for *Bos indicus*. GWAS of complex traits for Nelore cattle breed are important since there has no research reporting regions and genes associated to feed efficiency traits in this breed.

Keywords: *Bos indicus*; Feed efficiency; SNPs

Introduction

Feed efficiency has a major influence on the unit cost of beef production. Selection of efficient animals not only improves the producer's profitability, but can lead to significant reductions in the required pasture area per unit of production, decreased feed cost in feedlots, as well as, reduced environmental impact, through lower carbon and methane emissions. Residual feed intake (RFI) has been the most commonly used feed efficiency index and is defined as the difference between expected and predicted intake based on energy demands. However, RFI is independent of growth rate which may impact its acceptance by industry. Residual gain (RG) has also been proposed as a feed efficiency index which is represented as the residual from a multiple regression model whereby average daily gain (ADG) is regressed on both dry matter intake (DMI) and body weight (BW). A newly defined index-trait, residual intake and gain (RIG), combines RFI and RG, and can subsequently be used to identify efficient, fast growing animals, while still being independent of BW. The objective of this study was to identify genes/QTLs associated with RIG in Nelore cattle by genome wide association study using the BovineHD BeadChip (770 k) and Bayesian statistical approaches.

Materials and Methods

Animals and phenotypic data: A total of 593 Nelore steers with average of 382.5 kg, offspring's of 34 sires were used in this study. Calves were born on three different ranches, where they were raised to around 21 months old, before allocation to individual or collective pens in which individual feed intake data was measured in a feedlot system located in São Carlos, SP, Brazil; or in Campo Grande, MS, Brazil. Animals were fed ad libitum twice daily, with refusals about 5% daily. Diets contained 40% dry matter (DM) represented by corn silage (trial 1) or sorghum silage (trial 2); crude protein at 13.5% (trial 1), 15.4% (trial 2); energy densities of 2.8 (trial 1) or 2.6 Mcal metabolizable energy per kg DM (trial 2), 60% DM of concentrate, which contained ground corn, soybean meal, cotton seed (only trial 1), soybean grain (only trial 2), soybean hull, limestone, mineral mixture, urea and monensin (Rumensin®). The adaptation period was approximately 28 days and individual dry matter intake (DMI) was measured for at least 70 days with non-fasted body weight (BW) measured every 14 days. Individual DMI (kg/d) was obtained by the difference between offer and refusal and average daily gain (ADG, kg/d) was estimated by regression of body weight (BW) on days on feed using PROC REG (SAS, 2010). RFI(kg/d) was computed as the residual from regression of DMI on mid-test $BW^{0.75}$ and ADG (Koch et al., 1963) using mixed models, where contemporary group (CG), defined as a function of feedlot location, year, animal origin and pen type (individual or collective), was considered fixed effects by MIXED procedure (SAS, 2010). Residual gain (kg/d) was computed as the residual from regression of ADG on mid-test $BW^{0.75}$ and DMI, using the same procedures and effects used to calculate RFI. While, residual intake and gain (RIG) was calculated as the sum of -1*RFI and RG, both previously standardized to a variance of one.

DNA extraction and Genotypic Data: Genomic DNA was extracted from blood samples (Tizioto et al., 2012). Genotyping was performed with the BovineHD BeadChip, 770K (Illumina, San Diego, CA). The genotypes

Table 1: QTL region associated with residual intake and gain (RIG) in Nelore cattle.

Positional candidate genes	SNP Window (Start and end SNP)	Number SNP in Window	% Variance explained by SNP window	Chr	Map Position (UMD 3.1 bovine assembly)
PHKB VPS35 DNAJA2	rs109105703 -rs136356118	189	0.80	18	15002281…15989210

PHKB (phosphorylase kinase, beta), *VPS35* (vacuolar protein sorting 35 homolog), *DNAJA2* (similar to DnaJ (Hsp40) homolog, subfamily A, member 2).

were recorded in Illumina A/B allele format and transformed to a value of 0, 1, or 2, representing the number of B alleles present. Missing genotypes represented less than 0.2% of total observations and were replaced with the average number of B alleles for that locus. SNPs with call rate ≥ 95% and minor allele frequency (MAF) ≥ 5% were used in the analyses. SNPs in sex chromosomes and not mapped in the *Bos taurus* UMD 3.1 assembly were excluded. A total of 449,363 SNP were utilized in this study.

Genome Wide Association Study: The Bayes C methodology (Kizilkaya et al., 2010, Habier et al., 2011) was used to estimate the genetic and residual variances for use as priors in Bayes B. The Bayes C priors assumed genetic and residual variance equal to 1 and $\pi = 0.9997$. The GWAS between markers genotypes and phenotype (RIG) was undertaken with Bayes B (Meuwissen et al., 2001, Saatchi et al., 2013), based on the model equation:

$$\boldsymbol{y} = \mathbf{X}\boldsymbol{b} + \sum_{j=1}^{K} \boldsymbol{a}j\, \beta j \delta j \; + \; \boldsymbol{e}$$

where; **y** is a vector of phenotypic values, $\boldsymbol{X}$ is an incidence matrix for fixed effects, $\boldsymbol{b}$ is a vector of fixed effects representing contemporary groups, K is the number of SNP loci (449,363), $\boldsymbol{a}j$ is the column vector representing the SNP covariate at locus j coded as the number of B alleles, βj is the random substitution effect for locus j, which conditional on σ^2_β was assumed normally distributed $N(0, \sigma 2\beta)$ when $\delta j = 1$ but $\beta j = 0$ when $\delta j = 0$, with δj being a random 0/1 variable indicating the absence (with probability π) or presence (with probability $1-\pi$) of locus j in the model, and $\boldsymbol{e}$ is a vector of random residual effects assumed normally distributed $N(0, \sigma 2e)$. The parameter π was 0.9997 chosen to fit fewer markers than animals. The GWAS was conducted with GenSel software (Fernando et al., 2009), which uses MCMC methods to calculate posterior mean estimates of marker effects and variances. Genomic windows were constructed based on the chromosome and base pair positions denoted in a marker map file based on UMD-3.1. Some 2,527 SNP windows were used across the 29 chromosomes. Gensel samples the genetic variance based on the variance of samples of breeding values that are implied by the genotypes for each individual in product with the samples of each fitted locus. The proportion of variance explained by the markers is the ratio of the genetic variance divided by the sum of the genetic and residual variance. The SNP windows that explained >0.5% of genetic variance from Bayes B analysis were considered as QTL associated with traits. Positional candidate genes were identified using Gbrowse (http://www.animalgenome.org/gbrowse) in 1 Mb windows that explained >1% of genetic variance. The UMD-3.1 bovine assembly in Animal QTL database (http://www.animalgenome.org/QTLdb) and the Bovine QTL database (http://bovineqtl.tamu.edu/) were used to search for QTLs previously described in the literature. The functional classification of genes was performed using DAVID (Huang et al., 2009) and GO (Ashburner et al, 2000). Genes within 1 Mb windows and with biological function related to the trait were defined as positional candidate genes.

Results and Discussion

One genomic region, on BTA18 (at 15 Mb), explained 0.8% of genetic variance for RIG (Table1). The region has been previously reported to be associated with carcass weight in *Bos indicus* x *Bos taurus* cattle (Casas et al., 2003). Three genes have been annotated in this region; *PHKB* (phosphorylase kinase, beta), *VPS35* (vacuolar protein sorting 35 homolog), and *DNAJA2* (similar to DnaJ (Hsp40) homolog, subfamily A, member 2). *PHKB* has been associated with gene ontology terms: carbohydrate metabolic process (GO: 0005996), generation of precursor metabolites and energy (GO: 0006091) and energy reserve (GO: 0006112). *VPS35* and *DNAJA2* have gene ontology terms associated with protein localization and transport (GO: 0045184) and protein turnover (COG_ONTOLGY), respectively. This region on BTA18 seems to be important for feed efficiency traits in *Bos indicus* as it is associated with two additional feed efficiency traits, feed conversion ratio and feed efficiency (Oliveira et al., unpublished data). The positional candidate genes reported in this study have not been reported previously for this trait in *Bos indicus*. GWAS of complex traits for Nelore cattle are now emerging and should help to improve feed efficiency traits in Nelore.

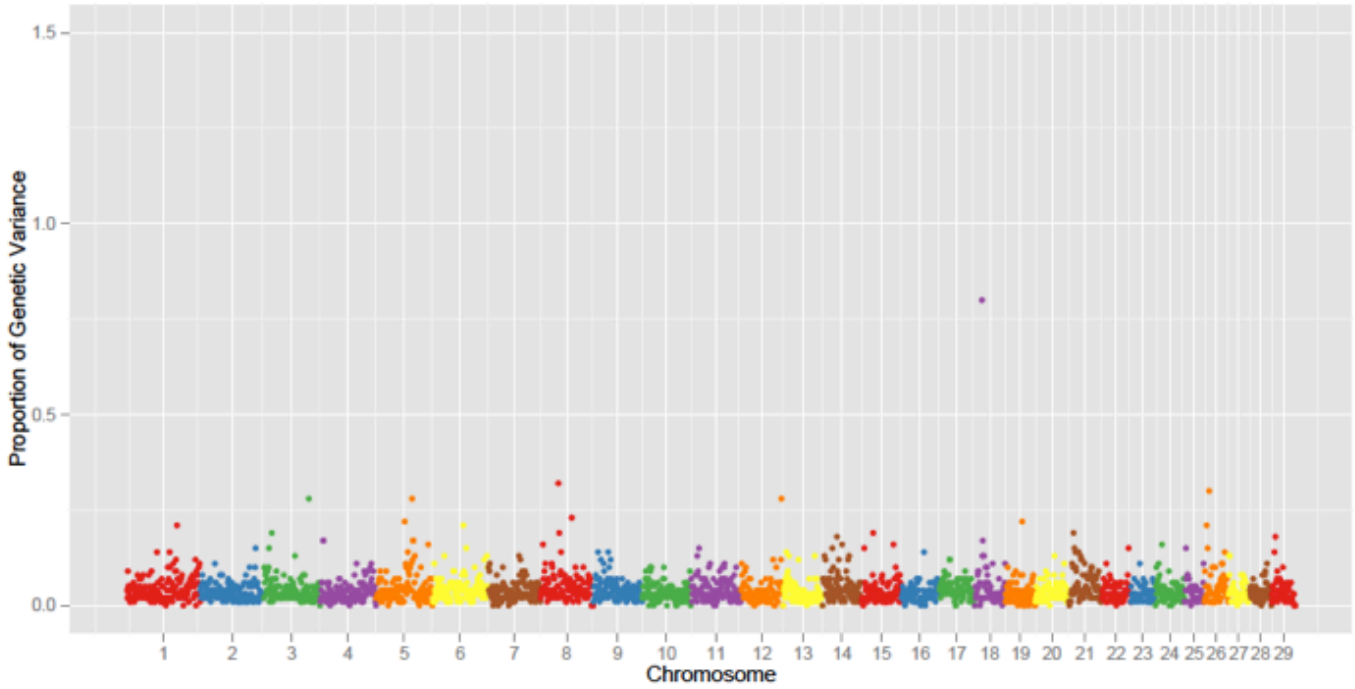

Figure 1. Manhattan plots of QTLs regions associated with residual intake and gain in Nelore cattle.
The X-axis represents the chromosomes, and the Y-axis shows the proportion of genetic variance explained by SNP window from Bayes B analysis

Conclusions

Genes within this region could be candidate genes for residual intake and gain in Nelore cattle. Once the genes and/or genomic segments that control feed efficiency related traits have been identified it should be possible to determine the biological mechanisms and the genetic basis that underlie these traits.

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