UNIVERSIDADE FEDERAL DE GOIÁS
ESCOLA DE VETERINÁRIA E ZOOTECNIA
PROGRAMA DE PÓS-GRADUAÇÃO EM ZOOTECNIA

ASSOCIAÇÃO E SELEÇÃO GENÔMICA PARA EFICIÊNCIA ALIMENTAR EM BOVINOS NELORE

Ludmilla Costa Brunes
Orientador: Prof. Dr. Cláudio Ulhoa Magnabosco

GOIÂNIA
2021

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LUDMILLA COSTA BRUNES

ASSOCIAÇÃO E SELEÇÃO GENÔMICA PARA EFICIÊNCIA ALIMENTAR EM BOVINOS NELORE

Tese apresentada para a obtenção do título de Doutor em Zootecnia junto à Escola de Veterinária e Zootecnia da Universidade Federal de Goiás.

Área de Concentração:
Produção Animal

Orientador:
Prof. Dr. Cláudio Ulhoa Magnabosco – Embrapa/CNPq/UFG

Comitê de orientação:
Prof. Dr. Fernando Baldi– UNESP/Jaboticabal
Dr. Fernando Brito Lopes – Cobb-Vantress

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Bibliografia. Anexos.
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ATA DE DEFESA DE TESE

Ata nº 48 da sessão de Defesa de Tese de **LUDMILLA COSTA BRUNES** que confere o título de **Doutora em Zootecnia** pelo Programa de Pós-Graduação em Zootecnia, na área de concentração em Produção Animal.

Aos vinte e dois dias do mês de fevereiro de dois mil e vinte e um - (22/02/2021) a partir das 14h00min, no auditório do Núcleo de Comunicação Organizacional (NCO) da Embrapa Arroz e Feijão, realizou-se a sessão pública de Defesa de Tese intitulada "**Associação e seleção genômica para eficiência alimentar em bovinos nelore**". Os trabalhos foram instalados pelo Orientador **Claudio Ulhôa Magnabosco** com a participação dos demais membros da Banca Examinadora: **Arthur dos Santos Mascioli - EVZ/UFG e Adriana Santana do Carmo – EVZ/UFG**, membro titular interno; **Marcos Fernando Oliveira e Costa - Embrapa Arroz e Feijão/Santo Antônio de Goiás e Alexandre Siqueira Guedes Coelho - EA/UFG**, membro titular externo. Durante a arguição os membros da banca não fizeram sugestão de alteração do título do trabalho. A Banca Examinadora reuniu-se em sessão secreta a fim de concluir o julgamento da Tese tendo sida a candidata Aprovada pelos seus membros. Proclamados os resultados pelo Orientador e Presidente da Banca Examinadora Claudio Ulhôa Magnabosco, foram encerrados os trabalhos e, para constar, lavrou-se a presente ata que será assinada pelos Membros da Banca Examinadora.

TÍTULO SUGERIDO PELA BANCA

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I'm fascinated by the idea that genetics is digital. A gene is a long sequence of coded letters, like computer information. Modern biology is becoming very much a branch of information technology.

Richard Dawkins

Sonhe com aquilo que você quer ser, porque você possui apenas uma vida e nela só se tem uma chance de fazer aquilo que quer. Tenha felicidade bastante para fazê-la doce. Dificuldades para fazê-la forte. Tristeza para fazê-la humana. E esperança suficiente para fazê-la feliz. As pessoas mais felizes não tem as melhores coisas. Elas sabem fazer o melhor das oportunidades que aparecem em seus caminhos. A felicidade aparece para aqueles que choram. Para aqueles que se machucam. Para aqueles que buscam e tentam sempre. E para aqueles que reconhecem a importância das pessoas que passaram por suas vidas.

Clarice Lispector

Aos meus pais Almir e Enia Brunes, pela força que me faz acreditar que tudo é possível, pelo amor incondicional a mim dedicado, por serem responsáveis pela minha maior formação, meu caráter, e por me ensinarem o valor da persistência, da fé, dos bons relacionamentos e da humildade. Vocês foram meu maior suporte...
A vocês dedico esta e todas as conquistas da minha vida.

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Se cheguei até aqui foi porque me apoiei no ombro de gigantes.

(Isaac Newton)

Muito obrigado!

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LISTA DE SIGLAS E ABREVIATURAS

ADG	Average daily gain
AFLP	Polimorfismo de comprimento de fragmentos amplificados
ANCP	Associação Nacional de Criadores e Pesquisadores
ANOVA	Analise de variância
ATP	Adenosine triphosphate
BF	Backfat thickness
BLASSO	Bayesian Least Absolute Shrinkage and Selection Operator
BLUP	Best Linear Unbiased Prediction
BTA	Bos taurus autosomes
BW	Birth weight
CA	Conversão alimentar
CAR	Consumo alimentar residual
cDNA	DNA Complementar
CG	Contemporary group
CGR	Consumo e ganho em peso residual
CMS	Consumo de matéria seca
CP	Crude protein
DAVID	The Database for Annotation, Visualization and Integrated Discovery
dDEP	Diferença esperada na progênie desregredida
DEBV	Deregresseded estimated breeding value
DIT	Days in teste
DM	Dry matter
DMI	Dry matter intake
DYD	Daughter-yield deviations
EA	Eficiência alimentar
EBV	Estimated breeding value
EG	Espessura de gordura
FCR	Feed conversion ratio
FE	Feed efficiency
GEBV	Genomic Estimated Breeding Value
GH	Growth hormone
GHR	Receptor do hormônio do crescimento
GMD	Ganho em peso
GO	Gene Ontology Consortium
GPR	Ganho em peso residual
GS	Genomic Selection
GSEA	Gene Set Enrichment Analysis
GTP	Guanosina trifosfato
GWAS	Genome wide Association Studies
HWE	Hardy-Weinberg equilibrium

IGF	Insulin-like growth factor
IGF-1	Insulin-like growth factor 1
IZ	Instituto de Zootecnia
KEGG	Kyoto Encyclopedia of Genes and Genomes
LD	Desequilíbrio de ligação
MAF	Minor allele frequency
MSE	Mean square error
$MW^{0.75}$	Metabolic body weight
PA	Prediction ability
PCA	Principal component analyses
PIB	Produto interno bruto
$PV^{0,75}$	Peso vivo metabólico
QC	Quality control
QTL	Quantitative trait loci
RAPD	Polimorfismo de DNA amplificados ao acaso
REA	Rib eye area
RES	Relative efficiency of selection
RF	Rump fat thickness
RFI	Residual feed intake
RG	Residual body weight gain
RIG	Residual intake and body weight gain
SC365	Scrotal circumference at 365 days of age
SC450	Scrotal circumference at 450 days of age
SD	Standard deviation
SNPs	Single nucleotide polymorphism
ssGBLUP	Single-step Genomic Best Linear Unbiased Prediction
TBV	True breeding value
TDN	Total digestible nutrients
UFG	Universidade Federal de Goiás
W120	Adjusted weight at 120 days of age
W240	Adjusted weight at 240 days of age
W365	Adjusted weight at 365 days of age
W450	Adjusted weight at 450 days of age
WssGBLUP	Weighted single-step Genomic Best Linear Unbiased Prediction
Y*	Fenótipo ajustado para efeitos fixos

RESUMO

Objetivou-se, com este estudo, estimar os parâmetros genéticos para características de eficiência alimentar, crescimento, reprodução e carcaça em rebanhos comerciais de bovinos Nelore, além da resposta correlacionada entre elas. Também objetivou-se realizar um estudo de seleção genômica avaliando métodos de predição, esquemas de validação e pseudo-fenótipos e conduzir um estudo de associação genômica ampla ponderado em passo único e análises de enriquecimento para características relacionadas à eficiência alimentar. Foram avaliados o consumo alimentar residual (CAR), consumo de matéria seca (CMS), conversão alimentar (CA), eficiência alimentar (EA), ganho em peso residual (GPR), consumo e ganho em peso residual (CGR), peso ao nascer (PN), peso aos 120 (P120), 240 (P240), 365 (P365) e 450 (450) dias de idade, perímetro escrotal aos 365 (PE365) e 450 (PE450) dias de idade, área de olho de lombo (AOL), espessura de gordura (EG) e espessura de gordura na garupa (P8). Foram utilizadas informações de crescimento, reprodução e carcaça de 15.639 bovinos Nelore. Foram utilizados dados de testes de eficiência alimentar realizados entre 2011 e 2018, com informações fenotípicas e genotípicas de 4.329 e 3.594 animais, respectivamente. Os parâmetros genéticos foram estimados utilizando método *single-step* (ssGBLUP). Seis métodos de predição dos valores genômicos (GEBVs) foram utilizados: ssGBLUP, Bayes A, Bayes B, Bayes Cπ, BLASSO e Bayes R. Três esquemas de validação foram utilizados: 1) aleatório: a base de dados foi aleatoriamente dividida em dez subconjuntos e a validação foi realizada em cada subconjunto por vez; 2) idade: a população foi dividida em treinamento e validação com base no ano de nascimento, sendo o primeiro grupo composto por animais nascidos entre 2010 a 2016 e o segundo nascido em 2017; 3) acurácia de predição do valor genético (EBV): foram divididos em dois grupos, sendo os animais com acurácia acima de 0,45 considerados como a população de treinamento; e abaixo de 0,45 a de validação. Foram avaliadas a acurácia e o viés de predição dos GEBVs. A porcentagem da variância explicada por janelas de 10 SNPs consecutivos foram usados para identificar regiões que explicam mais que 0,5% da variância genética aditiva de cada característica. As características relacionadas à eficiência alimentar apresentaram herdabilidades baixas a moderadas, variando de 0,07 a 0,20. As características relacionadas à eficiência alimentar apresentaram correlação genética baixa com crescimento (-0,19 a 0,24), reprodução (-0,24 a 0,27) e carcaça (-0,17 a 0,27), exceto para crescimento com CMS (0,32 a 0,56) e EA (-0,40). Os resultados demonstram que a habilidade de predição foi similares entre os métodos de predição. A baixa herdabilidade obtida, principalmente para EA (0,07±0,03) e CA (0,09±0,03), limitaram as acurácias dos GEBVs que variaram de baixa a moderada. Os coeficientes de regressão das estimativas foram próximos de 1, e similar entre os métodos de predição, esquemas de validação e pseudo-fenótipos. Em média e apesar da baixa variação (0,0331), a validação cruzada aleatória apresentou maior habilidade de predição, variando de 0,07 a 0,037, comparado a acurácia do EBV e idade. A habilidade de predição foi maior para o fenótipo ajustado para efeitos fixos do que para EBV e EBV desregredido (30,0 e 34,3%, respectivamente). As análises de enriquecimento com a ferramenta *The Database for Annotation, Visualization and Integrated Discovery* (DAVID) revelaram várias vias funcionais como via de sinalização de neuropeptídios (GO: 0007218), regulação negativa da via de sinalização Wnt canônica (GO: 0090090), detecção de estímulos químicos envolvidos na percepção sensorial do sabor amargo (GO: 0001580), atividade do receptor de sabor amargo (GO: 0033038), neuropeptídio atividade hormonal (GO: 0005184), secreção biliar (bta04976), transdução do paladar (bta0742) e via de sinalização de glucagon (bta04922). A seleção para melhorar características de crescimento, reprodução e carcaça pode não alterar CAR, GPR e CGR. Por outro lado, o CMS, EA e CA podem levar a um aumento do peso corporal, além da seleção para CA levar a uma redução no rendimento de carcaça. A natureza genética das

características relacionadas à eficiência alimentar pode levar a diferentes respostas genéticas. A escolha do critério de seleção mais adequado depende do sistema e dos objetivos de produção. Os métodos de predição genômica podem fornecer estimativas confiáveis dos valores genômicos para CAR, CMS, GPR e CGR, características que podem ter maior ganho genético e viabilidade de seleção comparada a EA e CA. As análises de enriquecimento mostraram genes associados ao metabolismo de insulina, leptina, glucose, proteína e lipídeo, balanço de energia, estresse oxidativo, sistemas *zinc fingers*, secreção biliar, saciedade, comportamento alimentar, salivação, digestão e absorção de nutrientes. A identificação das regiões genômicas e seus respectivos genes fornecem informações sobre bases genéticas e regulação biológica da eficiência alimentar em bovinos Nelore.

Keywords: *Bos indicus*, consumo alimentar residual, correlação genética, GWAS ponderado em passo único, valor genômico

ABSTRACT

The aim of this study was to estimate genetic parameters for feed efficiency, growth, reproductive and carcass traits in commercial Nelore cattle herds, and the correlated response between them. It was also aimed perform a study of genomic selection evaluating prediction methods, validation approaches and pseudo-phenotypes, and conduct a weighted single-step genome-wide association study and an enrichment analysis for feed efficiency of feed efficiency related traits. Residual feed intake (RFI), dry matter intake (DMI), feed conversion ratio (FCR), feed efficiency (FE), residual live weight gain (RG), residual intake and live weight gain (RIG), birth weight (BW), weight at 120 (W120), 240 (W240), 365 (W365), and 450 (W450) days of age, scrotal circumference at 365 (SC365) and 450 (SC450) days of age, rib eye area (REA), backfat thickness (BF) and rump fat thickness (RF) were evaluated. The growth, reproductive and carcass traits records from 15,639 Nelore cattle were used. Data from feed efficiency tests carried out between 2011 and 2018, with phenotypic and genotypic information of 4,329 and 3,594 animals, respectively, were considered. The genetic parameters were estimated in a single step approach (ssGBLUP). Six prediction methods of genomic breeding values (GEBVs) were used: ssGBLUP, Bayes A, Bayes B, Bayes Cπ, BLASSO, and Bayes R. Three validation approaches were used: 1) random: the data set was randomly divided into ten subsets and the validation was done in each subset at a time; 2) age: the population was divided into training and validation set based on the year of birth, with the first group consisting of animals born between 2010 and 2016 and the second group born in 2017; 3) genetic breeding value (EBV) accuracy: were divided into two groups, with animals with accuracy above 0.45 considered as the training population, and below 0.45 the validation set. We checked the accuracy and bias of GEBV. The percentage of variance explained by windows of 10 adjacent SNPs was used to identify regions that explained more than 0.5% of the additive genetic variance on each trait. The feed efficiency related traits showed low to moderate heritabilities, ranging from 0.07 to 0.20. Feed efficiency related traits showed low genetic correlations with growth (-0.19 to 0.24), reproductive (-0.24 to 0.27) and carcass (-0.17 to 0.27) traits, except for growth with DMI (0.32 to 0.56) and FE (-0.40). The results showed that the prediction ability were similar between the prediction methods. The low heritability obtained, mainly for FE (0.07±0.03) and FCR (0.09±0.03), limited the GEBVs accuracy, which ranged from low to moderate. The regression coefficient estimates were close to 1, and similar between the prediction methods, validation approaches, and pseudo-phenotypes. On average and despite low variation (0.0331), the random cross-validation presented the most accurate predictions, ranging from 0.07 to 0.037, than EBV accuracy and age. The prediction ability was higher for phenotype adjusted for fixed effects than for EBV and EBV deregressed (30.0 and 34.3%, respectively). Enrichment analysis by The Database for Annotation, Visualization and Integrated Discovery (DAVID) revealed several functional vias such as neuropeptide signaling pathway (GO:0007218), negative regulation of canonical Wnt signaling pathway (GO:0090090), detection of chemical stimulus involved in sensory perception of bitter taste (GO:0001580), bitter taste receptor activity (GO:0033038), neuropeptide hormone activity (GO:0005184), bile secretion (bta04976), taste transduction (bta0742), and glucagon signaling pathway (bta04922). The selection to improve growth, reproductive and carcass traits would not change RFI, RG, and RIG. On the other hand, DMI, FE and FCR may lead to an increase in body weight, in addition to the selection for FCR may lead to a reduction in carcass yield. The genetic background of feed efficiency related traits are different, which would lead to different genetic responses. The choice of the most adequate selection criterion depends on the production system and goals. Genomic prediction methods can provide a reliable estimate of

genomic breeding values for RFI, DMI, RG and RGI, traits that may have higher genetic gain and selection viability than FE and FCR. Enrichment analyzes showed genes associated with in insulin, leptin, glucose, protein and lipid metabolism, energy balance, heat and oxidative stress, zinc finger system, bile secretion, satiety, feed behavior, salivation, digestion and absorption of nutrients. The identification of these genomic regions and their respective genes provide information about genetic basis and biologic regulation for Nelore feed efficiency related traits.

Keywords: *Bos indicus*, genetic correlation, genomic breeding value, residual feed intake, weighted single-step GWAS

CAPÍTULO 1 – CONSIDERAÇÕES INICIAIS

1. INTRODUÇÃO

A bovinocultura de corte é uma das principais atividades do agronegócio brasileiro, apresentando o segundo maior rebanho efetivo e sendo um dos maiores produtores de carne bovina no mundo, com 232 milhões de cabeças e uma produção de 9,9 milhões toneladas de equivalente carcaça[1], sendo representado em 80% pela raça Nelore e seus cruzamentos[2]. Somente a pecuária foi responsável por aproximadamente 27,4% do produto interno bruto (PIB) do agronegócio[3], valor que representou 8,5% do PIB do Brasil em 2019[4]. A grande disseminação da raça Nelore para produção de carne em sistemas de criação tropical pode ser atribuída às suas características de adaptabilidade em diferentes condições de manejo, resistência aos parasitas, rusticidade e menor exigência de mantença comparada a animais taurinos[5,6].

Apesar dos números expressivos e grande potencial para produção de carne, o rebanho brasileiro e a raça Nelore vem sofrendo disputa, perdendo espaço para outras atividades produtivas mais rentáveis, isto porque, os índices econômicos dos sistemas de produção de bovinos ainda são considerados aquém dos desejáveis[7]. A saída para contornar esse fato está relacionada à busca de animais e sistemas de criação mais eficientes, como em relação aos insumos produtivos demandados e aos custos de produção, para que seja possível produzir carne de boa qualidade a um custo baixo[8].

Considerando que o custo despendido com alimentação chega a representar 80% dos custos totais de produção dependendo do sistema adotado, este componente é decisivo para a eficiência do sistema[9]. Assim, a utilização de animais mais eficientes quanto ao uso do alimento e a conversão deste em proteína pode incrementar os índices econômicos do sistema de produção, uma vez que o mesmo nível de produção poderia ser alcançado com um menor volume de insumo[9,10].

Dentre os caracteres comumente utilizados para avaliar os animais quanto à eficiência alimentar, destacam-se a eficiência alimentar (EA), propriamente dita; a conversão alimentar (CA); o consumo alimentar residual (CAR); o consumo de matéria seca (CMS); o ganho em peso (GMD); o ganho em peso residual (GPR); e o consumo e ganho em peso residual (CGR). Algumas dessas apresentam ressalvas ao serem utilizadas como critério de seleção genética, como a CA e EA, que podem estar geneticamente associadas ao peso adulto aumen-

tando as exigências de mantença dos animais ao longo das gerações e os custos de produção, como resposta à seleção[10–12]. O mesmo comportamento pode ser observado ao se utilizar como critério de seleção o GMD e o CMS, visto que, sem ajustes, conduzem à identificação de animais de maior tamanho corporal e exigência de mantença[12–14].

Nesse cenário, caracteres como o CAR, o GPR e o CGR trazem vantagens como critérios de seleção genética, pois apresentam independência fenotípica do peso adulto, tamanho corporal e exigência de mantença, além de possibilitar identificar os animais com menor consumo em relação ao predito baseando-se no peso e GMD; e maior ganho em relação ao predito baseando-se no peso e CMS dos animais, respectivamente, ou seja, possibilita identificar os animais mais eficientes quanto ao uso de alimento, sem afetar o desempenho[11,14–16].

Apesar de ser observada a existência da variabilidade genética, estimativas de herdabilidade que variam de moderada a alta e ausência de influência negativa no tamanho adulto e na exigência de manteça[12,16–18], a seleção genética para CAR, GPR e CGR tem apresentando como limitação o elevado custo e a dificuldade de mensuração[10,18]. Esse fato pode ser atribuído a necessidade de avaliação do CMS individual para o cálculo de medidas de eficiência alimentar. Ainda assim, a seleção para essas características resulta em animais com menor consumo de alimento para um mesmo nível de produção ou maior ganho para um mesmo nível de CMS, o que tem alto potencial de retorno econômico. Isso porque, os custos iniciais de implantação de sistemas para mensuração do CMS individual podem ser diluídos ao longo dos anos com o melhoramento genético e seleção de animais mais eficientes[18,19,20,21].

Considerando a difícil e onerosa mensuração de caracteres como o CAR, GPR e o CGR, o desenvolvimento de estudos com marcadores moleculares e informações genômicas, bem como o avanço das técnicas de sequenciamento e genotipagem apresentam grande importância para implementação de características relacionadas à eficiência alimentar nos programas de melhoramento genético[19,22].

Dentre as técnicas que incluem informação genômica na avaliação dos animais, está a seleção genômica (GS – *Genomic Selection*), que tem como objetivo explorar o desequilíbrio de ligação (DL) entre loci de características quantitativas (QTL – *quantitative trait loci*) e marcadores de polimorfismo de nucleotídeo único (SNPs - *single nucleotide polymorphism*) ao longo de todo o genoma, capturando parte importante da variação genética responsável pela variação fenotípica das características avaliadas, possibilitando, assim, se estimar o valor genômico dos animais (GEBV – *Genomic Estimated Breeding Values*)[23]. Dessa forma, na

seleção genômica é calculado o GEBV derivado dos SNPs e capturando o efeito de vários loci simultaneamente, para a seleção dos animais para as características de interesse econômico[23,24,25].

Na seleção genômica, uma população com dados de fenótipos e genótipos conhecidos é utilizada para formular uma equação de predição dos efeitos dos marcadores. Essa equação e as estimativas dos efeitos dos marcadores são, então, utilizadas para predizer GEBVs de animais de outra população, a de validação, com informação genotípica[25] e utilizando como variável resposta da equação informações fenotípicas ou um pseudo-fenótipo.

Tanto a metodologia adotada para a estimação quanto a validação e as variáveis respostas são de extrema importância para a acurácia de predição dos GEBVs e seleção dos animais[26]. Atualmente, vários métodos de regressão estão sendo avaliados como estimadores do valor genômico, apresentando vantagens e desvantagens de utilização e diferindo quanto a suposição da distribuição a priori dos efeitos dos SNPs[18,25,27–29]. Dessa forma, determinar qual a melhor estratégia para a estimação dos efeitos dos SNPs e predição dos GEBVs é um ponto crucial no processo de implementação da GS[30–32].

Os estudos de associação genômica (GWAS – *Genome-wide Association Studies*), que permitem identificar regiões genômicas associadas aos fenótipos, que atuam como marcadores moleculares, como os SNPs, e podem explicar parte importante da variância genética aditiva das características avaliadas[21,22,33]. Os resultados de GWAS podem ser expandidos através da identificação de vias metabólicas e análises funcionais que auxiliam no desenvolvimento de estratégias de seleção e maior compreensão da expressão fenotípica e da arquitetura genética, como a proporção da variância genética explicada pelos marcadores moleculares, que regem as características avaliadas, principalmente, as de alta complexidade biológica[21,23,34].

Como vantagens, a realização de estudos que abordam o uso de informação molecular pode reduzir o tempo de avaliação de características de difícil mensuração, como o CAR, GPR e CGR, aumentar a acurácia de predição dos valores genéticos, possibilitar a avaliação de animais ainda jovens ou mesmo na ausência de registro do seu próprio fenótipo ou de seus parentes e reduzir o intervalo de gerações, levando a maiores ganhos genéticos. Em adição, estudos de associação e seleção genômica podem contribuir significativamente para a identificação de mecanismos moleculares que influenciam a eficiência alimentar e que conduzem a variações no gasto de energia, permitindo avanços na área de melhoramento

genético animal, uma vez que auxiliam no estudo aprofundado de características com baixa resposta ao processo de seleção tradicional[18,35–37].

Ressalta-se que estudos genômicos têm sido mais expressivos em raças taurinas, de forma que, as informações obtidas podem não ser representativas para zebuínos, principal subespécie utilizada em sistemas brasileiros de produção de bovinos, pois esses estudos têm como base o DL entre marcador e uma variante causal e existem diferenças nas frequências alélicas e na extensão do LD entre estas subespécies[38,39]. Além disso, os estudos avaliando bovinos Nelore têm sido conduzidos, principalmente, com populações experimentais ou poucos rebanhos e de baixo tamanho amostral[35,13,40,41,12]. Adicionalmente, poucos são os estudos que avaliam as correlações genéticas entre características relacionadas à eficiência alimentar e outras características de importância econômica em bovinos Nelore, sobretudo com a inclusão de informação genômica[13,35,41–45].

Assim, faz-se necessária a realização de estudos de GWAS e GS que englobem raças zebuínas a fim de se conhecer a influência da seleção para eficiência alimentar sobre outras características comumente avaliadas em programas de seleção; melhorar a compreensão das variáveis específicas e identificação das variações estruturais nos genes ou regiões genômicas que influenciam características de difícil mensuração nesta subespécie; além de possibilitar a predição de valores genômicos acurados, garantindo maior assertividade na seleção de animais mais eficientes[38].

Nesse âmbito, objetivou-se estimar os parâmetros genéticos para características de eficiência alimentar e suas associações com características de produção, reprodução e carcaça em bovinos Nelore, além das respostas à seleção direta e correlacionada nessas características. Será avaliada a viabilidade da implementação da seleção genômica para características relacionadas à eficiência alimentar aplicando modelos de predição, esquemas de validação e pseudo-fenótipos, utilizando informações de rebanhos comerciais. Por fim, serão realizados estudos de associação genômica ponderada para detectar regiões genômicas e genes, além de análises de enriquecimento de genes para identificar processos biológicos e vias metabólicas compartilhadas por genes associados à eficiência alimentar em bovinos Nelore.

2. REVISÃO DA LITERATURA

2.1 Estado da arte da seleção genética para eficiência alimentar

Considerando o aumento da demanda da produção de alimento, incluindo produtos de origem animal, aliado à busca por sistemas de produção de maior sustentabilidade econômica e ambiental, a utilização de animais mais eficientes se torna cada vez mais desejável. Nesse âmbito, a eficiência alimentar é um importante índice a ser considerado na bovinocultura de corte, pois possibilita a identificação de animais com menor consumo de alimento em relação a quantidade de carne produzida. Uma vez que, a rentabilidade desses sistemas é dependente dos insumos utilizados e da receita obtida, considerando que o maior componente do custo de produção é o alimento fornecido, existe crescente interesse pela utilização de índices de eficiência alimentar[16,46].

A eficiência alimentar é importante, sobretudo para bovinos, uma vez que a maior parte da energia consumida é utilizada para suprir as exigências de mantença. Estima-se que 65 a 70% da energia metabolizável necessária para a produção de carne é destinada para os requerimentos de mantença[47]. Assim e apesar de animais Zebuínos terem menor exigência de mantença que Taurinos[6], a maior parte do alimento consumido é utilizada para mantença e não para o ganho em peso. Com isso, a redução dos custos destinados à alimentação de zebuínos envolve a redução das exigências de mantença.

A utilização de animais mais eficientes otimiza a produção de bovinos por aumentar a rentabilidade do sistema ao afetar diretamente a redução do consumo de alimento, além de reduzir o impacto ambiental ao diminuir o uso de insumos e recursos naturais, bem como a produção entérica de gases de efeito estufa e de dejetos sólidos, sem prejudicar o desempenho animal[13,15,16,19,28,48]. De acordo com DiLorenzo e Lamb[19], a seleção para eficiência alimentar, utilizando o CAR pode reduzir 29% da produção de esterco fresco e excreções de fósforo e nitrogênio, enquanto as emissões de metano podem ser reduzidas em até 28%.

A utilização de animais mais eficientes também contribuirá para minimizar o problema de competição por áreas produtivas, pois, de acordo com Basarab et al.[49], animais mais eficientes permitem a redução das áreas de pastejo, visto que nesses sistemas os animais consumirão menos forragem, sendo possível aumentar as taxas de lotação. O mesmo pode ser aplicado em sistemas de confinamento, pois será possível fornecer menos alimento para o mesmo nível de produção dos animais.

Em detrimento da importância econômica e ambiental das características de eficiência alimentar, os programas de melhoramento genético de bovinos de corte têm atribuído mais ênfase às características de crescimento, reprodutivas e de carcaça. Esse fato está relacionado à dificuldade e ao alto custo de mensuração para a coleta de informações em larga escala necessárias para estimação das características utilizadas como critério de seleção para eficiência alimentar, como o CMS individual, seja em sistemas de baias individuais ou coletivas providas de equipamentos capazes de mensurar está informação[12,21,38].

O desenvolvimento de tecnologias eletrônicas que permitem a mensuração do consumo individual de alimento automaticamente, tem facilitado a coleta de fenótipos para eficiência alimentar em bovinos[20]. Em adição, tem-se retorno dos custos necessários para a construção destes sistemas e/ou investimentos em mão-de-obra para mensuração do consumo individual, através da seleção e utilização de animais que consomem menos alimento apresentando o mesmo nível produtivo[21,50]. Ou seja, são observados benefícios econômicos com a seleção de animais mais eficientes e o melhoramento genético do rebanho ao longo dos anos, através da redução da quantidade de alimento utilizada, culminando no pagamento mais rápido do capital investido[21].

Tradicionalmente, a CA, a EA, o CMS e o GMD[14,16] têm sido utilizados para avaliação da eficiência alimentar. A EA é definida como uma razão entre o ganho em peso pelo CMS e mensurada em kg de GMD/kg de CMS. Já a CA, é o inverso, calculada como a razão do CMS pelo GMD e mensurada em kg de CMS/kg de GMD[11,15,16]. A seleção para CA, EA, CMS e GMD pode aumentar o peso adulto, elevando as exigências de mantença dos animais e, consequentemente, o custo de produção[22]. Além disso, o aumento do tamanho e peso adulto de vacas pode comprometer a eficiência reprodutiva, reduzindo o ganho no setor de cria[51].

Diante das desvantagens da utilização de caracteres como CA, EA, CMS e GMD e na busca por características que permitam a identificação de bovinos que possam converter os alimentos consumidos em proteína animal de forma mais eficiente, sem afetar negativamente características produtivas, reprodutivas e de carcaça, outras medidas têm sido propostas, entre elas o CAR, GPR e CGR. Estudos demonstram que a seleção utilizando estes indicadores (CAR, GPR e CGR) pode elevar a eficiência alimentar, além de não apresentar resposta correlacionada indesejável em outras características de importância econômica[11,22,52,53.] Além disso, a correlação genética entre características relacionadas à eficiência alimentar tem sido, de maneira geral, favorável. Com CA, por exemplo, tem sido observada estimativas de correlação genética com CAR de 0,45 a 0,85. De maneira semelhante, há correlação genética

positiva entre CMS e CAR, indicando que animais de CAR negativo consomem menos alimento[16,48]. As correlações genéticas entre CAR, GPR e CGR tem sido negativas e moderadas a altas (-0,34 a -0,90)[17,35].

O CAR (kg de MS/dia), proposto por Koch et al.[11], é estimado utilizando uma equação de regressão do CMS pelo GMD e peso vivo metabólico ($PV^{0,75}$), sendo a diferença entre o CMS observado e o predito, necessário para atender as exigências de manutenção e crescimento dos animais. O cálculo desta característica atribui independência fenotípica do peso adulto, do tamanho corporal e da taxa de crescimento. Essa equação faz do CAR um dos melhores índices para eficiência alimentar, pois leva em consideração o desempenho previsto e o ajuste do peso metabólico do indivíduo, além de indicar a variação genética da utilização de nutrientes. Os animais mais eficientes são aqueles que apresentam valores negativos para essa característica, pois tem menor consumo em relação ao estimado, mantendo o desempenho produtivo[49]. Tem sido demonstrado que animais mais eficientes avaliados pelo CAR em idades jovens, como a desmama, também apresentam CAR negativo em idades mais avançadas[15,16,46]. Estudos genéticos com CAR são recorrentes em raças taurinas, nos quais, as estimativas de herdabilidade variam de moderadas a altas magnitudes (0,28 a 0,64)[9,11,14,22,48,49,54]. Enquanto poucos trabalhos relatam estimativas de herdabilidade em zebuínos, ainda assim são observados valores moderados (0,18 a 0,37)[12,13,18,35].

O GPR (kg de GMD/dia) é obtido pela diferença entre o ganho em peso individual observado e o predito através de uma equação de regressão composta pelo CMS e o $PV^{0,75}$ [11]. Desta forma, permite a identificação dos animais que apresentam crescimento mais rápido, consumindo menos alimento que o esperado e sem apresentar diferenças no peso vivo. Para GPR, o desejado são valores positivos, indicando possibilidade de atingir maior ganho em peso que o esperado para o peso corporal e o CMS. Assim como o CAR, o GPR é baseado no CMS e independente do crescimento e do tamanho adulto. O GPR foi proposto como uma alternativa para a seleção de animais mais eficientes, e que não seja independente do ganho em peso, o que ocorre com o CAR. Esta pode ser uma das razões para que o CAR não seja extensamente adotado em programas de seleção, uma vez que animais de crescimento lento podem ser considerados eficientes quando apresentam CAR negativo[22]. A avaliação do GPR tem sido ainda menor que o CAR. Com isso, poucas estimativas de herdabilidade têm sido relatadas para essa característica, as quais variam de 0,29 a 0,62 para taurinos[11,17] e de 13 a 0,40 para zebuínos[13,28].

Enquanto a baixa associação do GMD pode ser um problema para o CAR, a baixa associação do CMS pode ser um empecilho na utilização do GPR[22,41]. Dessa forma, foi proposta um caractere obtido da combinação entre o CAR e o GPR, que é o CGR. Esse caractere é estimado para ser independente do tamanho adulto e também apresentar uma relação favorável e equilibrada entre CMS e GMD[22,41]. O CGR é obtido através da diferença entre CAR e GPR padronizadas para terem variâncias iguais a um. Com isso, os animais com valores positivos são os mais eficientes e desejáveis[22]. O CGR, assim como o CAR, apresenta independência do peso metabólico, porém apresenta correlação fenotípica negativa com a ingestão de alimentos e positiva com ganho em peso. Assim, espera-se que a seleção realizada para CGR reduza a probabilidade de um animal de crescimento lento ter classificação favorável para eficiência alimentar, pois possibilita a identificação de animais que apresentem maiores ganhos em peso e menor consumo, sendo economicamente mais vantajosos[22]. Em animais taurinos, a herdabilidade relatada para CGR é de 0,36±0,06, sendo um valor intermediário entre as herdabilidades para CAR e GPR[55]. Para bovinos Nelore, as estimativas de herdabilidade relatadas para CGR variam de 0,11±0,06 a 0,15±0,05[13,41].

Além das correlações favoráveis com as características de crescimento, estudos relatam que a seleção para eficiência alimentar pode levar à melhoria no desempenho de características como a musculosidade e conformação de carcaça[17,22,28,35]. Isso devido à correlação genética favorável do CAR com as características de carcaça, como área do músculo *Longissimus dorsi*, peso da carcaça e características musculares[56]. Porém, estudos divergentes relatam baixa correlação entre CAR, CGR e características de carcaça, variando de -0,03 a 0,17 para bovinos Nelore e Angus[35,57] e entre GPR e características de carcaça, variando de -0,10 a 0,14 em taurinos[55].

Contudo, a seleção para eficiência alimentar, principalmente, baseada no CAR pode reduzir a proporção de gordura subcutânea na carcaça[28], sendo que animais mais eficientes tendem a apresentar carcaça com maior proporção de tecido muscular, porém mais magras e com menor grau de acabamento, devido ao CAR estar relacionado fenotipicamente com a composição corporal[14,49,58]. Isto pode afetar negativamente a qualidade de carne, a precocidade sexual e o desempenho reprodutivo dos animais, bem como a rentabilidade do sistema, sendo esta uma limitação para adoção do CAR[8,19,46,48,52,59].

Por outro lado, têm sido observado resultados divergentes de estudos indicando mudanças na composição do ganho, sendo que, em sua maioria, a associação genética entre CAR, qualidade de carcaça e precocidade sexual tem sido pequena. Esse fato é atribuído a

diferenças na idade de mensuração das medidas associadas à eficiência, maturidade fisiológica e na curva de crescimento entre os animais avaliados, o que afeta a composição do ganho corporal, taxa de metabolismo e maturidade reprodutiva[16,21,49,53,58]. Com isso, para a seleção de bovinos de corte, são necessárias estratégias para aumentar a eficiência alimentar, mas sem prejudicar características de desempenho ou associadas a qualidade final do produto[12]. Diante destes resultados, propôs-se a estimação do CAR e do GPR incluindo na equação a espessura de gordura (EG), corrigindo assim, o viés para a composição da carcaça e reduzindo a correlação entre essas medidas de EG. Com isso, os animais são classificados com base no consumo estimado para a mesma composição do ganho, tornando o CAR, GPR ou o CGR independente da característica para a qual foi ajustado. Como vantagem adicional, quando essas características são ajustadas para EG não são observadas diferenças nos índices reprodutivos, como a taxa de prenhez e reconcepção[49,54,60]. De fato, baixas correlações genéticas têm sido relatadas entre CAR estimado incluindo EG e perímetro escrotal (-0,03 a 0,07) em bovinos Nelore e outras raças de bovinos de corte[57,61].

Em detrimento da relevância da mensuração do consumo de matéria seca e da avaliação da eficiência alimentar, os avanços obtidos através do melhoramento clássico permitiram singelo progresso genético. Visto que, além da dificuldade de mensuração, ainda é um desafio se estimar o valor genético de animais jovens e com alta acurácia para essas características. A utilização de estudos que englobam informações genômicas, aliada aos métodos tradicionais de melhoramento genético, pode ser uma alternativa para contornar essas limitações.

2.2 Estudos genômicos e marcadores moleculares

No âmbito da genética animal, o fenótipo da maioria das características de importância econômica tem herança poligênica, ou seja, são controladas por um grande número de genes. Para esse grupo de características, as quantitativas, os loci que afetam a sua expressão são denominados QTLs[62]. Os estudos que abordam QTLs levaram ao desenvolvimento de marcadores moleculares, que são regiões do genoma, sequências de DNA ou genes identificados através de polimorfismos genéticos[62]. As técnicas de biologia molecular existentes e o sequenciamento de genomas permitiram o desenvolvimento de uma série de marcadores moleculares, como os microssatélites, polimorfismo de DNA amplificados ao acaso (RAPD), polimorfismo de comprimento de fragmentos amplificados (AFLP), polimorfismo de nucleotídeo único (SNP), entre outros[62].

Dentre esses, marcadores do tipo SNP, definidos como uma alteração em uma única sequência de base, em outras palavras, o sítio no genoma onde um par de bases difere gerando dois alelos para um marcador específico, se mostraram mais promissores se tornando preferenciais sobre outros tipos de marcadores moleculares. Isso porque representam diversidade da sequência genômica, baixa taxa de mutação, são mais polimórficos, metodologia de fácil aplicação e automatização, alta acurácia e desempenho, além do baixo custo. Os SNPs podem estar diretamente associados à expressão fenotípica quando ele é a mutação causal, alterando a regulação e/ou a expressão do gene, ou indiretamente associado quando se encontra ligado à mutação causal, devido ao desequilíbrio de ligação. Este, por sua vez (o LD), é uma associação não aleatória entre alelos de diferentes loci[63]. As informações de marcadores em LD com QTL podem ser utilizadas como fontes de variação de mérito genético e, assim, aplicadas na identificação de indivíduos candidatos à seleção, aumentando a acurácia de avaliação genética[64].

O sequenciamento do genoma bovino possibilitou o desenvolvimento de painéis de genotipagem de alta densidade e que contém um grande número de marcadores moleculares do tipo SNP distribuídos ao longo do genoma. Com o avanço das metodologias genômicas, painéis de menor densidade e menor custo têm se tornado preferidos pelos melhoristas. Apesar da menor densidade, esses painéis contêm SNPs mais informativos[65], sendo capazes de capturar grande parte da variação genética responsável pela expressão de características[66].

2.2.1 Métodos de predição do valor genômico e sua aplicação em características associadas a eficiência alimentar

A seleção genômica é um método que permite incluir informações de marcadores moleculares na avaliação genética dos animais, baseando-se no uso de um conjunto denso de marcadores SNPs, que cobre todo o genoma. A GS contempla três etapas: estimação e validação do modelo de predição, predição dos valores genéticos dos candidatos à seleção e seleção dos indivíduos baseados nas predições[24,25]. Para tal, uma população (de referência) com dados de fenótipos e genótipos conhecidos é utilizada para se estimar uma equação de predição dos efeitos dos marcadores de DNA simultaneamente, combinando informações fenotípicas, sendo essas equações regressões entre fenótipos e genótipos que permite estimar o efeito da substituição dos alelos de cada marcador[67]. Esta equação composta pela combinação do genótipo dos SNPs e as estimativas dos efeitos dos marcadores são, então, utilizadas para predizer GEBVs de animais de outra população (de validação), com informação genotípica,

mas que não precisam necessariamente possuir dados fenotípicos, pois pseudo-fenótipos podem ser utilizados, como o valor genético estimado (EBV), EBV desregredido (DEBV – *Deregresseded estimated breeding value*), o fenótipo ajustado para efeitos fixos (Y*). Após validada, esta equação pode ser utilizada para predizer os GEBVs dos candidatos a seleção. Assim, a soma de todos os efeitos SNPs é utilizada como preditor do mérito genético dos animais avaliados[24,25].

Apesar de muitos marcadores terem sido associados à eficiência alimentar, ainda não foram descritos genes com efeito maior para essas características[67–69], o que é explicado pela natureza poligênica das mesmas, sendo influenciadas por muitos genes com efeito pequeno. Nesse sentido, a combinação dos marcadores moleculares, considerando as regiões genômicas de alto e baixo efeito para predição genômica pode ter maior potencial para explicar a variância genética de características poligênicas, aumentando a acurácia de avaliação.

Ao combinar informações fenotípicas, de pedigree e genômicas, é possível aumentar a acurácia de avaliação dos animais, principalmente, para características que se expressam em um único sexo ou de forma tardia, de alto custo de mensuração e/ou que sejam de baixa herdabilidade. Além disso, a GS permite a realização da predição genômica de caraterísticas e a seleção de animais jovens, antecipando o processo de identificação e reduzindo o intervalo de geração, o que diminui os custos de avaliação e aumenta o ganho genético[26]. Outra vantagem da GS é a predição do mérito genético dos animais, mesmo sem a mensuração dos seus próprios fenótipos ou de parentes mais próximos[67], uma vez que pseudo-fenótipos podem ser utilizados. Assim, a seleção genômica permite otimizar o ganho genético de várias características de importância econômica e difícil mensuração, incluindo as mesmas como rotina de avaliação em programas de seleção e intensificando o uso de animais geneticamente superiores, incluindo aqueles ainda jovens[70].

Vários métodos de estimação dos efeitos dos marcadores têm sido estudados e comparados, a fim de se encontrar o mais adequado quanto a habilidade de predição dos valores genômicos para diferentes características. No entanto, não há consenso entre as pesquisas sobre a metodologia mais adequada para cada característica. A metodologia e distribuição mais adequada para a estimação dos efeitos dos QTLs ou marcadores são condicionadas à característica avaliada, visto que o número de QTLs e a proporção da variância genética explicada pelos marcadores variam juntamente com a mesma[32]. Com isso, a escolha do método mais apropriado pode ter impacto direto na acurácia das predições genômicas, que além de ser dependente da distribuição dos efeitos dos QTLs, depende da quantidade de informação

fenotípica, densidade e tipo de marcadores utilizados e herdabilidade da característica[25,26,67]. Esses métodos variam em relação a distribuição *a priori* dos efeitos dos marcadores, que podem ser obtidos assumindo que todos os SNPs contribuem igualmente para a variância genética ou assumindo que a distribuição prévia dos efeitos do marcador e/ou QTL não segue distribuição normal[25,31,71,72.]

Considerando um banco de dados nos quais os fenótipos, genótipos e pedigree estão disponíveis, um método simples e prático para incorporação de informações genômicas é pelo BLUP genômico (GBLUP - *Genomic Best Linear Unbiased Predictor)*. Com este procedimento, a matriz de parentesco baseada no pedigree (A) é combinada com uma matriz de parentesco genômico (G), considerando informações dos marcadores SNPs, formando a matriz conjugada H[26]. O objetivo é obter soluções para as equações de modelos mistos utilizando uma matriz que combina informações da matriz de parentesco aditivo, modificada pelas contribuições da matriz de parentesco genômico[73]. Apesar da complexidade para a criação da matriz H, este é um método viável até mesmo para um grande conjunto de dados[73]. Além disso, a única informação *a priori* para a realização deste método é uma estimativa da variância genética da característica avaliada, eliminando a necessidade de vários parâmetros e suposições[32].

O GBLUP foi aprimorado em uma metodologia de etapa única e de acurácia semelhante ao BLUP tradicional e os métodos de múltiplas etapas[73,74], formando o ssGBLUP (*Single-step Genomic Best Linear Unbiased Prediction*). As avaliações genômicas utilizando ssGBLUP apresentam acurácia semelhante aos procedimentos de várias etapas, além de trazer como vantagens a avaliação de animais genotipados e não genotipados em conjunto, a utilização de fenótipos em vez de pseudo-fenótipos e levar em consideração toda a estrutura populacional para se estimar o GEBV[73]. Em situações em que a matriz de parentesco da população em estudo é incompleta, a utilização de pseudo-fenótipos para estimação dos efeitos dos SNPs para predição dos GEBVs pode não ser acurada. Dessa forma, a utilização de ssGBLUP pode ser vantajosa ao aumentar a confiabilidade das avaliações, por informar a proporção de fragmentos compartilhados pelos indivíduos com a matriz genômica, corrigir erros de genealogia, identificar relações de parentesco desconhecidas e diferenciar o parentesco entre irmãos completos. Com isso, essa metodologia reduz o erro advindo do parentesco obtido pela informação de pedigree incompleto ou incerto, além de ser mais precisa que a matriz de parentesco convencional[26,75]. Esse método também é adequado para análises multi-

características e permite a predição indireta de valores genéticos em animais jovens através dos efeitos dos SNPs com acurácia de uma avaliação completa[74].

Em contrapartida, o método ssGBLUP estima todos os efeitos do marcador simultaneamente e segue distribuição normal, com média zero e variância igual para todos os SNPs[75]. Com isso, pode haver superestimação da variância de marcadores sem efeito e subestimação dos de alto efeito, levando à baixa acurácia e sendo essa uma desvantagem desse método[67]. Considerando o fato de que assumir que todos os efeitos dos SNPs são normalmente distribuídos com uma variância constante pode ser irreal[67], as predições genômicas também podem ser obtidas considerando diferentes pressuposições no modelo. Neste âmbito, estão as metodologias Bayesianas, que assumem muitos tipos de distribuições *a priori* para as variâncias e os efeitos dos SNPs, considerando que pouquíssimos SNPs tem efeito muito alto e a maioria dos SNPs tem efeito pequeno ou nulo, ou seja, assumem que os marcadores podem explicar diferentes proporções da variância genética da característica analisada[26].

Essas abordagens consistem em se estimar o valor genômico predito (GEBV – *Genomic breeding value*) por um índice que combina o EBV e o valor genômico direto (DGV), ao utilizar informações *a priori* dos parâmetros a serem preditos com as informações do banco de dados disponíveis, gerando uma distribuição *a posteriori* para cada parâmetro do modelo. Métodos bayesianos se baseiam na informação a *priori,* o que pode influenciar as estimativas finais dos efeitos dos marcadores, uma vez que, geralmente, o número de animais é muito menor do que o número de efeitos de marcadores a se estimar. Para que as distribuições *a posteriori* sofram mínima influência das informações *a priori*, faz-se necessária a utilização de um banco amplo e representativo da raça ou espécie avaliada. Ainda assim, resultados apresentados na literatura apresentam vantagens dos modelos bayesianos sobre o GBLUP[67].

Meuwissen et al.[25] apresentaram duas metodologias Bayesianas, BayesA e BayesB, as quais apresentam simplicidade de implementação e vantagens de utilização, visto que cada *locus* apresenta uma variância individual e explora melhor o LD entre SNPs e QTL[30–32]. Logo, essas metodologias podem levar a estimativas de GEBVs mais acuradas. Para tal, assume-se, *a priori*, que o efeito do SNP é zero com probabilidade π, e apresentam uma distribuição normal com média zero e variâncias *locus*-específicas com probabilidade $(1 - \pi)$, permitindo uma cauda mais longa na densidade da curva, sendo possível identificar genes com efeito de moderado a alto. A distribuição das variâncias *locus*-específicas é qui-quadrado invertida escalonada, com poucos graus de liberdade e com um parâmetro de escala derivado de uma variância genética

aditiva previamente assumida, sob pressuposições genéticas variáveis. Em ambos métodos, π deve ser tratado como desconhecido e, portanto, estimado[25].

Para BayesA e BayesB, a probabilidade π de um SNP ter efeito nulo é considerada conhecida. No método BayesA, assume-se que as variâncias diferem para cada SNP e a probabilidade π é tratada como zero, para que nenhum SNP tenha efeito nulo. Já para BayesB, é permitido que muitos marcadores possam ter efeito igual a zero, assumindo uma distribuição *a priori* com efeito dos SNPs igual a zero com probabilidade π e os demais com variância locus-específica com probabilidade (1- π). Considerando que o número de QTL pode ser menor que o número de marcadores e o grande número de SNPs nos painéis de genotipagem atuais, é esperado que alguns marcadores não apresentem efeito, sendo esta uma vantagem do BayesB. Além disso, no BayesB, π apresenta probabilidade maior que zero para concordar com a pressuposição de que muitos SNPs apresentam efeito nulo.

De acordo com Gianola[76], as distribuições *a posteriori* das variâncias locus-específicas das metodologias BayesA e BayesB apresentam apenas um grau de liberdade a mais quando comparadas com a distribuição *a priori*, independentemente do número de genótipos e/ou fenótipos utilizados. Essa limitação tem ainda mais destaque com o aumento da densidade de SNPs[31]. Além disso, o método de BayesB utiliza Algoritmo Metropolis Hastings, que demanda um grande tempo computacional, comparado a outros métodos baseados em amostragem de Gibbs[77].

Uma das metodologias que foi desenvolvida para contornar esse problema foi o BayesCπ[31], que busca reduzir a influência da distribuição *a priori*, considerando variância comum para todos os SNPs e *prioris* não informativas; além da estimativa de π, a proporção dos SNPs com efeito nulo é obtida a partir dos dados, porque este parâmetro influencia o *shrinkage* dos efeitos dos SNPs. O que difere de BayesA e BayesB, os quais assumem π como sendo conhecido. A estimativa da variância a partir dos dados, pode ser considerada uma desvantagem quando o número de animais é baixo, comparado aos milhares de efeitos a serem estimados. Ainda assim, esses valores são menos dependentes da *priori* que no BayesB[78]. Além disso, no BayesCπ, os efeitos dos SNPs seguem uma distribuição qui-quadrado invertida escalonada *a priori*, com ν_g graus de liberdade e um parâmetro de escala S_g^2, sendo assim, o efeito de um SNP utilizado com probabilidade (1-π) é uma mistura de distribuições t de Student $t\ (0, \nu_g, S_g^2)$. Para o parâmetro π assume-se distribuição uniforme a *priori*. Dessa forma, essa pode ser uma metodologia viável para a estimação dos efeitos dos marcadores e aplicação na seleção genômica, por levar em consideração a arquitetura genética da característica e

identificar as posições de QTLs por modelagem da frequência de marcadores com efeito diferentes de zero[31].

Outro método comumente aplicado para GS é o Lasso Bayesiano (BLASSO – *Bayesian Least Absolute Shrinkage and Selection Operator*), proposto por Tibshirani[79] como Lasso e modificado por Legarra et al.[80]. Nesse método assume-se distribuição dupla exponencial para o efeito dos SNPs, sendo esse próximo de zero e com variâncias individuais. Por outro lado, no método Lasso original, uma moda conjunta é estimada e espera-se que a maioria dos marcadores tenham efeitos iguais a zero, no BLASSO são estimadas médias *a posteriori*, produzindo valores diferentes de zero. Além disso, esse método produz um *shrinkage* específico de acordo com o efeito e variância do marcador. O BLASSO consiste em dividir as fontes de variação em um termo puramente residual (σ_e^2) e um devido aos SNP (σ_g^2). Esse método apresenta como vantagem em relação a BayesA e BayesB, ser menos influenciado pela informação *a priori*.

Uma crítica a métodos como BayesB é que a proporção de SNPs em cada distribuição não é amostrado adequadamente, de forma que as médias das distribuições da proporção de SNPs com efeito igual a zero ou diferente de zero reflete os valores a *priori* destas proporções[31]. Para contornar essa desvantagem e reduzir o custo computacional, Erbe et al.[72], desenvolveram um método que pressupõe que os verdadeiros efeitos dos SNPs são derivados de uma série de distribuições normais para modelar os efeitos dos SNPs de forma flexível, possibilitando que eles variam de 0 a valores mais altos. Esse modelo, denominado BayesR, utiliza uma abordagem de Monte Carlo baseado em cadeias de Markov (MCMC) para estimar os efeitos das variantes causais, que são modelados como uma distribuição mista de quatro distribuições normais incluindo uma distribuição nula, N (0, $0.0\sigma^2_g$), e três outras: N (0, $0.0001\sigma^2_g$), N (0, $0.001\sigma^2_g$), N (0, $0.01\sigma^2_g$), em que σ^2_g é a variância genética aditiva para a característica. A primeira distribuição acomoda a probabilidade de que muitas variantes não tenham efeito sobre a característica, reduzindo assim a complexidade do modelo. Esse modelo apresenta semelhante poder de predição e mapeamento a métodos lineares e outros bayesianos[72].

Com base nos testes realizados por Erbe et al.[72], sugere-se que BayesR apresenta vantagens em estudos com maiores densidades de marcadores, por ser o método que possibilita remover uma proporção dos SNPs menos relevantes do modelo de predição ou que fazem ajustes dos efeitos para zero. Em BayesR, a proporção de SNPs em cada distribuição normal é estimada a partir dos dados, em vez de ser pré-definida como um valor constante, o que ocorre

em BayesB. Com isso, BayesR é capaz de aproximar uma ampla gama de possíveis distribuições verdadeiras de efeitos SNP, além de apresentar menor custo computacional que BayesB[77]. O BayesR também apresenta a possibilidade de utilizar os resultados (SNPs em diferentes classes de variância) para análises posteriores como arquitetura genética ou seleção de subconjuntos de SNPs para análise de predição que serão menos exigentes em termos computacionais.

Atualmente, a maioria dos estudos de GS têm sido focados na comparação de metodologias quanto a habilidade de predição dos GEBVs. Tal como o estudo de Pryce et al.[81], no qual foram realizadas predições genômicas para CAR em novilhas australianas e os autores encontraram uma vantagem na acurácia das predições genômicas obtidas usando modelos bayesianos, como o BayesA, sobre o GBLUP. Os autores levantaram a hipótese de que os métodos bayesianos devem fornecer maior acurácia de predição quando alguns SNP estão em LD com QTL de tamanho grande a moderado.

Chen et al.[82], avaliaram predição genômica para CAR em bovinos das raças Angus e Charolês utilizando três métodos estatísticos (BLUP, GBLUP e BayesB). Considerando a raça Angus como população de treinamento e validação, os autores reportaram acurácias de 0,58; 0,54 e 0,53 para os modelos GBLUP, BLUP e BayesB, respectivamente. Considerando a raça Charolês como população de treinamento e validação, os autores reportaram acurácias de 0,64; 0,62 e 0,38 para os modelos BayesB, GBLUP e BLUP, respectivamente. A superioridade do método GBLUP em relação ao método BLUP tradicional, foi atribuída à capacidade do primeiro método em capturar o LD entre o QTL e os marcadores, além da melhor captura da relação genética, em comparação a matriz de parentesco baseada apenas no pedigree. Já as diferenças entre os métodos BayesB e GBLUP são atribuídas à arquitetura genética da característica, sendo que o BayesB pode superar o GBLUP quando existem QTLs de maior efeito afetando a característica dentro da raça avaliada, já o GBLUP apresenta predições com acurácia mais alta quando há um número grande de QTLs de efeito pequeno dentro da raça avaliada[82]. Assim, raças de diferentes tipos biológicos e com distribuição dos efeitos dos marcadores distintas também podem se adequar melhor a diferentes métodos de predição genômica.

Bolormaa et al.[83], avaliando a acurácia de predições genômicas para características de eficiência alimentar (CAR, CMS, GMD) em animais *Bos taurus*, Brahman, compostos e cruzados, utilizando BayesR e GBLUP, observaram acurácias médias de 0,27 considerando todas as raças e características avaliadas, sendo que os valores obtidos por BayesR foram em

média 0,03 maiores do que as acurácias obtidas com GBLUP, com superioridade de até 0,23. Em adição, os autores ressaltam que o BayesR possibilitou a identificação de muitos loci de características quantitativas, porém, o mapeamento ocorreu com maior acurácia e com maior efeito atribuído a SNPs perto das mutações causais. Além disso, características com grande número de registros fenotípicos e genótipos, bem como alta herdabilidade apresentaram maior acurácia para os GEBVs[83].

A acurácia de predição e a escolha do método de GS é dependente da arquitetura genética da característica, pois conforme apresentado por Wang et al.[84], se uma pequena quantidade de loci apresentam grande efeito sobre uma característica, observa-se maior diferenças entre a capacidade de predição de vários métodos (RR-BLUP, BayesA, BayesB, BayesCπ e BLASSO), sendo que neste cenário, BayesCπ foi recomendado. Se a característica é controlada por um moderado número de genes, a diferença entre os métodos é menor, ainda assim, neste cenário BayesA se mostrou mais preciso e mais flexível, adaptando-se bem a diferentes números de QTLs. Por fim, se uma característica é controlada por um grande número de genes de efeito pequeno, o que ocorre para a maioria das características de importância econômica, Wang et al.[84], não observaram diferenças significativas na capacidade de predição dos métodos avaliados.

Em bovinos da raça Nelore, Silva et al.[50], avaliando os métodos BLUP tradicional, GBLUP, ssGBLUP e BayesCπ para características CAR, GMD, CA e CMS em bovinos Nelore, apresentaram acurácias médias variando de 0,10 a 0,58 usando BLUP, de 0,09 a 0,48 usando GBLUP, de 0,06 a 0,49 usando BayesCπ e de 0,22 a 0,49 usando ssGBLUP, observando que o ssGBLUP forneceu predições de maior acurácia do que os métodos de múltiplas etapas, principalmente, para características de baixa herdabilidade. Os autores atribuem esses resultados a inclusão de informações fenotípicas de animais não genotipados em combinação as informações genotípicas e fenotípicas dos animais genotipados, com aumento de 15% dos animais avaliados, bem como ao fato deste método considerar as informações das relações de parentesco entre os animais, em vez de considerar o animal de forma individual. Os resultados apresentados por Silva et al.[50] também demonstram que à inclusão de informações dos marcadores podem aumentar a acurácia de predição, em relação ao BLUP tradicional, principalmente para características de baixa herdabilidade como o CAR. Outro ponto destacado por Silva et al.[50], foi que usando BayesCπ são obtidos valores acurados, principalmente para características de baixa herdabilidade (CAR=0,17 e CA=0,11).

Assim, diversos fatores intrínsecos à característica, como a distribuição dos efeitos dos SNPs, a poligenia, a variância genética e a herdabilidade; bem como fatores relacionados as informações disponíveis, como número de amostras, raças, painel de genotipagem, número de animais com genótipos e fenótipos, entre outros podem afetar a habilidade de predição dos modelos genômicos. Dessa forma, é importante avaliar a metodologia adequada para definição de equações de predição dos GEBVs para características de eficiência alimentar em populações comerciais e diferentes rebanhos de bovinos Nelore.

2.2.1.1 Métodos de validação das equações de predição genômica

Conforme mencionado, na GS é utilizada uma equação de predição dos valores genômicos que passa por uma validação. Além disso, as equações de predição genômica não podem ser validadas nos mesmos animais utilizados para prevê-la[50], assim a população avaliada precisa ser dividida entre animais de treinamento e validação. Dentre os métodos de validação disponíveis, estão validação cruzada e baseado em parâmetros como idade dos animais e acurácia de avaliação.

Em pesquisas científicas, a validação e habilidade de predição dos valores genômicos têm sido, principalmente, verificada por meio da técnica de validação cruzada aleatória[72,78]. Este método é um esquema de validação robusto e não paramétrico para seleção de um modelo. Para tal, o conjunto de dados é divido em subconjuntos de referência e de validação, sendo estes de tamanho aproximado. A equação de predição é definida baseando nos conjuntos de referência e utilizada para predizer as observações do conjunto de validação, sendo este procedimento repetido até que todos os subconjuntos sejam utilizados como treinamento e validação[78].

O método de validação cruzada aleatória é indicado para base de dados quando há baixa estruturação dos dados, poucas gerações registradas ou quando as acurácias dos EBVs são baixas para serem aplicadas em previsões futuras[78]. Contudo, nesse método, os subconjuntos são formados de maneira aleatória ou por *clusters* e, em certos casos, pode resultar na formação de subconjuntos com alto grau de parentesco entre os animais, viesando a acurácia de predição[85]. De acordo com Pérez-Cabal et al.[86], as relações genéticas entre os indivíduos têm um grande efeito sobre a acurácia de predição. Pryce et al.[81], avaliando CAR e peso à desmama em novilhas Holandesas, também observaram que a acurácia de predição genômica é influenciada pelo parentesco entre os indivíduos e quanto maior o nível de parentesco genômico entre os animais, mais acurados são os valores genômicos preditos.

Em condições práticas, um ponto importante da aplicação da seleção genômica é possibilitar a predição do mérito genético da próxima geração, utilizando apenas a informação genômica. Nesse sentido, animais mais velhos podem ser utilizados como população de referência para definir as equações de predição a serem validadas em animais mais jovens, sem fenótipos e com a utilização de pseudo-fenótipos ou com poucas informações, sobretudo para características de difícil ou alto custo de mensuração[31,87]. Uma vez que assim, seria possível aplicar a GS à nível de grandes populações e rebanhos comerciais. Outro método de validação que também permite essa aplicação, é a divisão dos subconjuntos pela acurácia do EBV, sendo a população de treinamento os animais com maior acurácia e de validação de menor[31,87].

Com esses métodos, os animais mais jovens ou com menor acurácia do EBV podem ser testados por descendência e, assim, têm GEBVs mais confiáveis. Além disso, essas equações podem ser utilizadas para populações com diferentes relações genéticas entre os candidatos à seleção[85]. Por outro lado, diferenças entre o tamanho das populações de treinamento e validação podem influenciar na acurácia de predição[88]. Além disso, o número de gerações que separam os subconjuntos de treinamento e validação, que pode apresentar maior variação na validação por idade ou acurácia do EBV, também influencia a acurácia de predição[89].

Silva et al.[50], avaliando características de eficiência alimentar em bovinos Nelore, observaram maior acurácia de predição genômica para o método de validação cruzada aleatória em comparação a validação por idade e por grupos menos aparentados, atribuída à maior proporção de relações aditivas entre as populações e a menor relação dentro das populações no primeiro método e também pelo menor número de gerações que separam as populações. Em adição, segundo Silva et al.[50], métodos de validação cruzada permitem a obtenção de subconjuntos com animais de diferentes gerações, o que permite validar o modelo em parentes próximos, animais da mesma geração e do mesmo rebanho. Contudo, nesse mesmo estudo[50], a acurácia de predição obtida pelo método de validação pela idade foi superior ao método considerando indivíduos não relacionados por parentesco e para as características CMS e GMD foi semelhante ao método de validação cruzada, atribuída à maior herdabilidade obtidas para essas características. Assim, o método de validação pela idade pode ser um esquema viável e preciso para a predição do desempenho das gerações futuras, principalmente para características de alta herdabilidade.

Assim, não há consenso sobre o esquema ideal de validação das equações de predição genômica e o desenho ideal de populações de referência e validação, que irá depender

da população, da relação de parentesco dos animais e dos parâmetros genéticos da característica avaliada, entre outros fatores.

2.2.1.2 Variáveis-resposta utilizadas na predição genômica

Um importante parâmetro nas análises de GS é a variável resposta utilizada ou pseudo-fenótipo. Para tal, o valor genético real (TBV – *True breeding value*) seria o parâmetro ideal. Porém, ele é desconhecido e outros valores têm sido avaliados para este fim. Em populações onde todos os animais possuem informações de genótipo e fenótipo, a utilização dos próprios fenótipos nas predições genômicas pode ser viável[23]. Contudo, esse cenário raramente é observado em grandes populações e/ou rebanhos comerciais. Assim, a utilização de outros pseudo-fenótipos mais informativos pode ser requerida. Dentre as opções, destacam-se: o EBV, DEBV, Y*, a diferença esperada na progênie desregredida (dDEP), o desvio da produção das filhas (DYD – *daughter-yield Deviations*)[88,90].

Para populações que apresentam EBV com baixa acurácia de predição, a utilização do DEBV como pseudo-fenótipo é desincentivada. Isso porque, nessas condições o DEBV incorpora muitos "ruídos" durante o processo de desregressão, em que a contribuição dos pais é removida[37]. Além disso, para bases de dados com pedigree ausente, a desregressão do EBV pode ser viesada[91].

Em cenários onde grande quantidade de informação esteja disponível para o cálculo do EBV, este pode ser um preditor mais confiável do mérito genético dos indivíduos[90]. Para características de baixa herdabilidade, a utilização de EBV como pseudo-fenótipo pode resultar em maior acurácia de predição que Y*[85]. Por outro lado, a utilização do EBV traz como problemas a heterogeneidade das variâncias resultantes de EBVs preditos por diferentes quantidades de informação, como em rebanhos onde os touros possuem números diferentes de progênie[90], sendo o DEBV um pseudo-fenótipo que corrige essas limitações[92]. Para base de dados nas quais a quantidade de informação utilizada para prever EBV for pequena e for observado maior heterogeneidade entre os animais de referência, a utilização do DEBV também pode ser preferível.

O Y* tem sido indicado quando a população amostral é pequena ou de baixa confiabilidade para estimar o EBV[50,85]. Esse pseudo-fenótipo tem mostrado superioridade quanto a acurácia de predição comparado ao EBV, principalmente para características de alta herdabilidade e pequenas populações[85]. Diferentes pseudo-fenótipos apresentam diferentes sinais de natureza genética que afetam os resultados obtidos e a habilidade de predição dos

modelos[88]. Assim, o pseudo-fenótipo utilizado vai depender da estrutura do banco de dados avaliado[23].

Irano[93], avaliando precocidade sexual em bovinos Nelore, observaram maior acurácia de predição e menor grau de inflação/deflação utilizando DEBV como variável resposta em comparação ao EBV. Por outro lado, Fernandes Junior et al.[85], avaliando características de carcaça em bovinos Nelore, observaram acurácias de predição utilizando EBV 22% (área de olho de lombo) e 11% (peso da carcaça quente) mais baixas do que a utilização do Y*, indicando vantagem em se utilizar o fenótipo ajustado ao invés do EBV como variável resposta para características de maior herdabilidade. Ainda neste estudo, para espessura de gordura que foi a característica de menor herdabilidade, o EBV demonstrou maior vantagem ao ser utilizado como variável resposta[85]. Costa[94], avaliando características reprodutivas em bovinos Nelore, observaram acurácias de predição do fenótipo ajustado superiores ao EBV e DEBV.

Em função do limitado número de estudos com bovinos Nelore e da importância da eficiência alimentar sobre os índices econômicos e produtivos em sistemas de produção de bovinos, é primordial o desenvolvimento de trabalhos de seleção genômica para eficiência alimentar em bovinos. Além disso, é importante identificar metodologias de seleção genômica, esquemas de validação e os pseudo-fenótipos para aplicação nas condições de produção de bovinos no Brasil, a fim de se identificar os modelos que melhor se enquadram para estimação dos GEBVs de características de eficiência alimentar e em condições tropicais, que diferem das condições de países de clima temperado e das raças taurinas, em que a maioria dos estudos genômicos vem sendo conduzidos.

2.2.2 Estudos de associação genômica ampla e sua aplicação em características associadas à eficiência alimentar

Os GWAS, que têm como objetivo a exploração de loci ou de regiões genômicas, cuja as variações no DNA, principalmente SNPs, estão associadas a variância genética aditiva e a diferenças fenotípicas entre os animais. Esse tipo de estudo tem como pressuposição o desequilíbrio de ligação entre pelo menos um marcador e um polimorfismo de efeito maior ou QTLs responsáveis por uma proporção da variância genética e da fenotípica observada. Para esse fim, estima-se a correlação entre a variação genotípica observada em um marcador ou gene candidato e a variação de uma característica avaliada[62], sendo a correlação significativa quando há LD entre o marcador e o locus[64,95]. Ressalta-se que, em sua maioria, características de

interesse para sistemas de produção de bovinos apresentam base genética complexa, sendo influenciadas por um grande número de loci de pequeno efeito, ou seja, explicam uma pequena proporção da variância genética quando analisados isoladamente[23]. Dessa forma, várias regiões genômicas ou marcadores podem ser identificados associados a expressão fenotípica de características, apontando para a localização e identificação de genes ou segmentos genômicos relacionados as mesmas, possibilitando a incorporação dessas informações nas avaliações dos animais[12,27,97–100,29,33,38,40,48,68,95,96].

Os resultados obtidos nos estudos de GWAS são utilizados para auxiliar na compreensão dos mecanismos biológicos e da arquitetura genética de características poligênicas, tendo, principalmente, vantagens no auxílio da avaliação de características de difícil ou elevado custo de mensuração ou avaliadas tardiamente[32,95]. Essas informações são de grande importância para incorporação em programas de melhoramento genético, por permitir modelar os efeitos dos marcadores, aumentando a acurácia de avaliação dos valores genéticos, otimizando o ganho genético[25].

A utilização de métodos estatísticos capazes de detectar com precisão as associações genômicas é o ponto crítico da realização de estudos de GWAS, principalmente, porque em alguns métodos realiza-se a comparação de centenas de milhares de SNP, um a um, o que aumenta as taxas de faltos positivos ou erro tipo I[101].

Pela simplicidade e praticidade aliadas à acurácia, metodologias que consideram os SNPs na avaliação em um único passo se tornaram promissoras para estudos de GWAS, sendo amplamente utilizados em estudos com bovinos, tal como o ssGBLUP[73]. Método *single-step* GBLUP possuem, como principal vantagem, a possibilidade de combinar simultaneamente em uma única etapa todas as informações disponíveis, que são os fenótipos, pedigree e genótipo (marcadores SNPs) e utilizar inclusive animais sem genótipo para formação de uma matriz de parentesco, incluindo informação genômica ao invés de matriz clássica baseada apenas no pedigree. A inclusão de animais não genotipados nas análises pode aumentar a acurácia de identificação de QTL associados às características avaliadas[75]. Este método gera soluções de equações dos modelos mistos que serão utilizadas para investigar as potenciais regiões genômicas envolvidas com a expressão fenotípica da característica avaliada[52].

O ssGBLUP baseia-se no modelo infinitesimal, que assume igual variância para todos os efeitos dos SNPs e é uma limitação para utilização desta metodologia, uma vez que esta não é a real situação para todas as características de interesse econômico, que apresentam marcadores com efeitos mais pronunciados que outros[52]. Como forma de superar esse problema,

foi proposto o ssGBLUP ponderado (WssGBLUP - *Weighted single-step Genomic Best Linear Unbiased Prediction*), que também combina informações de fenótipos dos animais genotipados e não genotipados, bem como dos seus pedigrees, eliminando a necessidade de calcular pseudo-fenótipos e atribuindo pesos diferentes para os marcadores de acordo com sua suposta relevância, através de um processo iterativo, atualizando as soluções dos efeitos dos SNPs e melhorando a detecção de QTLs[102,103].

Assim, como em métodos bayesianos, o WssGBLUP permite uma distribuição desigual das variâncias associadas a cada loci, possibilitando identificar QTLs com efeitos pequenos a grandes, resultando em maior acurácia na estimativa dos efeitos dos SNPs. Neste método, os GEBVs dos animais genotipados obtidos pelo ssGBLUP são convertidos para os efeitos dos SNPs. Outra vantagem do WssGBLUP é a possibilidade de se trabalhar com janelas SNP, uma vez que uma janela de SNPs consecutivos nos GWAS pode ter mais sucesso na identificação de regiões com QTL em comparação com a análise de SNPs individuai por causa do LD. Além disso, a proporção da variância genética explicada por SNPs identificada via GWAS[97] é baixa, devido à complexidade genética das características quantitativas, as quais são afetadas por uma grande quantidade de locus de pequeno efeito[23]. Assim, é um método adequado para características complexas, como as quantitativas; para análise de múltiplas características ou para situações onde há muitos animais com fenótipo disponível, mas poucos genótipos, comuns em populações comerciais[102,103].

Recentemente, o número de estudos de associação genômica com características associadas a eficiência alimentar em bovinos tem aumentando, principalmente utilizando raças taurinas, possibilitando a identificação de diversas regiões cromossômicas associados a essas características e também identificação dos processos que mais contribuem para a variação da mesma.

Barendse et al.[96] avaliaram 189 touros de sete raças diferentes (Angus, Brahman, Belmont Red, Hereford, Murray Grey, Santa Gertrudis, e Shorthorn) e estimando a proporção da variância explicada pelo SNP significativo por meio de regressão, encontrando 161 SNPs que representam 141 regiões do genoma bovino relacionadas com o CAR. Nkrumah et al.[104], avaliando 400 bovinos das raças Angus, Charolês e cruzados, identificaram QTLs localizados nos cromossomos 1, 5, 7, 8, 12, 16, 17 e 26 associados ao CAR; nos cromossomos 5, 6, 7, 11, 14, 16, 17, 18, 19 e 28 associados a GMD; nos cromossomos 1, 3, 15, 17, 18, 20 e 26 para CMS; e nos cromossomos 3, 5, 7, 11, 16, 17, 22, 24 e 28 associados a EA. Sherman et al.[68], avaliando 400 bovinos das raças Angus, Charolês e animais compostos, encontraram 19

cromossomos contendo QTLs associados ao CAR, 12 associados a CA e quatro associados ao CMS, considerando como nível de significância o valor de p de 0,05 e em regiões semelhantes as apresentadas por Nkrumah et al.[104]. Sherman et al.[69], avaliando 2663 bovinos *Bos taurus* e compostos, encontraram 23 SNPs significativamente (P<0.05) associados com o CAR, formando um painel de SNPs que teve efeito significativo na eficiência alimentar, explicando 36,5% da variação do CAR para essa população e em regiões semelhantes as apresentadas por Barendse et al.[96] e Sherman et al.[68].

Bolorma et al.[97] avaliaram associações genômicas para CAR, peso corporal e altura de garupa em diferentes grupos genéticos (*Bos indicus, Bos taurus e B. indicus x B. taurus*), utilizando dados de genótipos dos SNPs obtidos com chips de 10K e 50K e janelas de SNPs individuais. Nesse estudo, os autores encontraram 27 marcadores do tipo SNP significativos (p<0,001) para CAR em 24 cromossomos, em todas as raças e em ambos painéis. Dos achados de Bolorma et al.[97], os SNPs mais significativos foram detectados nos *Bos taurus autosome* (BTA) 3, 5, 7 e 8. Os SNPs detectados nos BTAs 8, 11, 17, 18, 21, 22, 24, 25 e 26 por Bolorma et al.[97] estão próximos aos relatados por Sherman et al.[68] e Nkrumah et al.[104] associados a CAR.

Mujibi et al.[98], avaliando 728 bovinos compostos e das raças Angus e Charolês, utilizando regressão de marcador único, encontraram 34, 35 e 44 SNPs associados (P < 0,05) ao CAR, GMD e CMS, que explicaram 16,1; 17,1 e 7,29% da variância fenotípica, respectivamente. Avaliando 3887 novilhos da raça Angus e associação genômica considerando EBVs ponderados pelas suas respectivas acurácias, Rolf et al.[33] encontraram 66, 53 e 68 SNPs associados ao CAR, CMS e GMD (P < 0,05), que explicaram 62,69; 54,12 e 55,13% da variância genética aditiva, respectivamente. Seabury et al.[99], trabalhando com características de crescimento e eficiência alimentar para 698 animais das raças Angus, Hereford e SimAngus e utilizando modelo linear misto implementado em EMMAX, detectaram 14 regiões genômicas para as características de CAR, CMS, GMD e peso metabólico, considerando a proporção estimada de variância explicada pelos efeitos do marcador (1,0%) e valor de p de (P ≤ 0,00005).

Santana et al.[38], avaliando a associação genômica com CMS e CAR em 720 bovinos Nelore e utilizando analise de associação baseada em métodos de componentes de variáveis Grammar-Gamma e janelas de SNPs individuais, identificaram dois SNPs localizados nos cromossomos 8 e 21 associados ao CAR, 10 SNPs localizados nos cromossomos 3 e 10 associados ao GMD e três SNPs localizados nos cromossomos 4, 8 e 14 associados ao CMS, respectivamente, considerando –log do valor de P, corrigido para o ajuste de Bonferroni como limite de significância. Regiões genômicas semelhantes às relatadas por Santana et al.[38]

associadas ao CAR, também foram relatadas por Bolorma et al.[97], Sherman et al.[68] e Nkrumah et al.[104] avaliando animais taurinos.

Olivieri et al.[12] avaliando características de eficiência alimentar em 896 bovinos Nelore usando método de associação genômica em passo único, encontraram oito janelas, compostas por 10 SNPs consecutivos, que explicaram mais de 1% da variância genética aditiva associadas ao CMS, 12 janelas para CAR, 14 para eficiência alimentar e 18 janelas para GMD. Para GMD, as regiões genômicas significativas estavam presentes nos BTAs 1, 3, 5, 6, 10, 12, 14, 15, 16, 17, 18, 21, 25 e 27. Para CAR, as regiões genômicas significativas estavam presentes nos BTAs 1, 4, 7, 8, 10, 11, 18, 20, 21, 22 e 27. Para CMS, as regiões genômicas significativas estavam presentes nos BTAs 4, 9, 11, 15, 18 e 22[12].

Avaliando 593 bovinos Nelore e utilizando abordagem bayesiana, Oliveira et al.[40] identificaram seis (BTAs 1, 3, 7, 9, 14 e 16), três (BTAs 9, 13 e 24), quatro (BTAs 12, 15, 18 e 20), quatro (BTAs 1, 2, 9 e 14) e quatro (9, 11, 18 e 21) janelas genômicas de 1 Mb que representavam mais de 1,0% da variância genética associadas a GMD, CMS, CA, EA, CAR, respectivamente. Neste estudo, a variação genética explicada por janelas individuais de QTL para características de eficiência alimentar variou de 0,5% a 9,07%.

Avaliando duas populações com um total de 1137 bovinos Nelore de dois programas de avaliação genética (Instituto de Zootecnia e Nelore Qualitas) com a metodologia ssGBLUP, Santos[100] identificou regiões genômicas constituídas por 100 SNPs consecutivos e que explicaram pelo menos 1% da variância genética aditiva localizados nos cromossomos 1, 5, 6, 7, 8, 10, 13 e 14, que explicaram 23,15 e 16,45% da variância genética para CA, no Instituto de Zootecnia (IZ) e Qualitas, respectivamente. Para CAR, Santos[100] identificou 18 regiões que explicaram 17,73% e 7,98% da variância genética aditiva nos rebanhos IZ e Qualitas, respectivamente. Para CMS, Santos[100] identificou 14 regiões que explicaram 17,42 e 16,49% da variância genética nas populações IZ e Qualitas, respectivamente. Para EA, Santos[100] identificou 10 regiões localizadas que explicaram 26,07% e 9,06% da variância genética aditiva no IZ e Qualitas, respectivamente.

QTLs e regiões genômicas relatados na literatura indicam algumas das regiões específicas de baixo efeito que controlam fenótipos para CAR e outras características associadas a eficiência alimentar. Contudo, poucos são os GWAS que avaliaram GPR e CGR. Além disso, diferentes regiões genômicas têm sido associadas com as mesmas características em diferentes populações[12,40,38,97,100,68,96,104,69]. Essas diferenças estão relacionadas a variações entre raças e no desequilíbrio de ligação entre SNPs e variáveis causais[105], as falsas associações

entre fenótipos ocasionadas pelo pequeno número de amostras disponíveis nos estudos[98,106], além de poderem estar associadas a variação na metodologia, critérios de seleção dos SNPs e efeitos utilizados no ajuste de informações fenotípicas.

Ainda assim, os resultados obtidos de GWAS indicam que os SNPs associados as características indicadoras de eficiência alimentar, muitas vezes, diferem das demais características de importância econômica[12,38,40,100]. Após validação, o uso de SNPs identificados podem ser utilizados para formação de painéis de marcadores e para estimação dos valores genéticos moleculares e DEPs genômicas. Além disso, as regiões genômicas e SNPs identificados nos estudos de GWAS podem ser avaliados em análises de enriquecimento de vias metabólicas e funcionais, identificando assim as funções dos genes identificados associados a características de interesse[107], além de auxiliar no maior conhecimento sobre a distribuição e novas hipóteses de controle ou expressão.

2.2.2.1 Análises de prospecção de genes e enriquecimento de vias metabólicas e funcional

O passo seguinte às análises de GWAS, é a investigação das regiões associadas aos fenótipos de interesse, quanto a suas funções biológicas e vias metabólicas, elucidando os mecanismos biológicos e genéticos das características avaliadas[107]. Considerando que cada estudo de GWAS tem grande poder para detectar variantes relacionadas a características complexas e detectam por volta de 50 SNPs mais significativos e seus genes vizinhos, que representam apenas uma fração da variância genética[95,102], é importante utilizar esses resultados para a identificação de genes associados à regulação dessas características, aumentando o poder do mapeamento associativo. Essas análises são denominadas análises de enriquecimento (GSEA – *Gene Set Enrichment Analysis*) e permitem inferir a funcionalidade de uma longa lista de genes derivados dos estudos de GWAS, fornecendo interpretação dos mecanismos biológicos destes genes, informação essencial para o estudo dos processos fisiológicos que influenciam os fenótipos[108].

Várias metodologias e ferramentas foram desenvolvidas a fim de investigar as listas de SNPs significativos enriquecidos em genes que constituem uma via metabólica ou têm regulação em comum, utilizando informações disponíveis nos bancos de dados biológicos que auxiliam na compreensão dos resultados obtidos no GWAS[109]. Essas ferramentas são utilizadas para avaliar a frequência dos termos funcionais da lista de genes, aplicando testes estatísticos para determinar aqueles termos significativamente representados ou enriquecidos[108]. Informações provenientes de bancos como *Gene Ontology Consortium* (GO)[110], a Enciclopédia de Genes e Genomas de Kyoto (KEGG - *Kyoto Encyclopedia of Genes and Genomes*)[111] e Ensembl[112] são utilizados nesse contexto. Além destas, o DAVID (*The Database for Annotation, Visualization and*

Integrated Discovery)[109] é uma ferramenta que pode ser utilizada para facilitar a consulta de informações presentes nas bases de dados disponiveis publicamente.

Uma ferramenta comumente utilizada, é o sistema de anotação de gene Ensembl Biomart, através de um alinhamento automatizado que se baseia nas sequencias biológicas, como o cromossomo e a posição inicial e final de cada região significante identificada no GWAS. A avaliação cuidadosa dessas sequencias permite a formação de um conjunto final de genes com suas respectivas identificações e posições, ligando as sequências genômicas às suas funções biológicas. O processo de anotação com essa ferramenta apresenta alto rendimento, velocidade e consistência, com a anotação de milhares de genes em paralelo[112].

Dentre as ferramentas mais populares está o DAVID[109], que permite a integração de diversos bancos de dados simultaneamente e utilizando algoritmos avançados de análise de enriquecimento, que visam extrair sistematicamente o significado biológico das grandes listas de genes e proteínas. A análise funcional no DAVID utiliza o teste de Fisher modificado (EASE score) para agrupar genes e proteínas especificas provenientes de diversos bancos de dados públicos como o NCBI, PIR e Uniprot/SwissProt. Essa ferramenta possibilita organizar um grande conteúdo de anotações heterogêneas, como termos GO, domínios proteicos e vias metabólicas em classes gênicas.Com auxílio deste banco é possível fazer a identificação, classificação dos genes quanto à função biológica, análise de vias metabólicas e enriquecimento de genes[113]. O DAVID fornece recursos como um banco de dados integrado e com anotação *back-end* expandida e capacidade exploratória em um ambiente integrado de mineração de dados[114,115].

Ao longo dos anos, o GWAS levou à descoberta de importantes genes relacionados a características associadas à eficiência alimentar. Tal como o estudo de Barendese et al.[96], no qual foram analisados genótipos de touros de sete raças diferentes (Angus, Brahman, Belmont Red, Hereford, Murray Grey, Santa Gertrudis, e Shorthorn) e encontraram genes localizados em regiões genômicas associadas ao CAR que desempenham funções relacionadas a reguladores da utilização de energia na célula, incluindo processos como apoptose, progressão celular, canais iônicos e fluxo, transcrição, tradução, crescimento e desenvolvimento; além de genes envolvidos com a homeostase, regulação de apetite e controle de massa corpórea.

Sherman et al.[68], identificaram genes localizados em regiões genômicas associadas ao CAR, em bovinos das raças Angus, Charolês e animais compostos, como o gene para o receptor do hormônio do crescimento (GHR) e regiões cromossômicas que codificam proteínas associadas a moduladores de apetite (grelina e neuropeptídeo Y). Sherman et al.[69], avaliando

bovinos *Bos taurus* e compostos, encontraram genes localizados em regiões genômicas associadas ao CAR com funções celulares relacionadas ao controle do ciclo celular, metabolismo e olfato. Mujibi et al.[98], avaliando bovinos compostos e das raças Angus e Charolês, identificaram genes localizados em regiões genômicas associados ao CAR que desempenham funções como metabolismo de aminoácidos e proteicos, respostas imunológicas, canais de cátions, proteínas *zinc finger*, componentes de membranas. Rolf et al.[33], avaliando bovinos da raça Angus, encontraram genes localizados em regiões associados ao CAR, cujas funções estão relacionadas a processos metabólicos, crescimento e a eficiência de utilização de energia. Na pesquisa de Seabury et al.[99], avaliando animais das raças Angus, Hereford e SimAngus, identificaram genes localizados a regiões genômicas associadas ao CAR que produz a fonte enzimática conhecida de riboflavina, associado ao metabolismo oxidativo de carboidratos, aminoácidos e ácidos graxos; além dos associados à recuperação celular.

Em bovinos Nelore, Santana et al.[38] identificaram genes localizados em regiões genômicas envolvidas com o CAR ligados a processos de transporte iônico e ao gasto energético de ruminantes, semelhante ao resultado apresentado por Barendse et al.[96]; e o gene que codifica o neuropeptídio Y também relatado por Sherman et al.[68] associado ao CAR. Ainda na pesquisa de Santana et al.[38] foi identificado gene que codifica o hormônio leptina, estes estão associados com o controle de apetite, o gasto energético e o metabolismo da gordura e glicose. Também em bovinos Nelore, Oliveira et al.[40], encontraram dois genes candidatos posicionais e funcionais associados ao CAR e que desempenham funções associadas a degradação e o *turnover* proteico, ao metabolismo de ácidos graxos e a biossíntese lipídica. Santos[100], através de análises de enriquecimento em bovinos Nelore, identificou genes associados ao CAR com funções relacionadas ao transporte de íons e codificação de proteínas de ligação do tipo *Zinc Fingers*, proteínas codificadas que dependem de íons de zinco para estabilidade, canais de potássio, receptores sensoriais, proteínas de membrana com funções biológicas associadas a processos celulares, tais como transcrição, secreção celular e transporte através de membranas. Algumas das vias metabólicas relatadas por Santos[100] avaliando bovinos Nelore também foram observadas por Mujibi et al.[98] avaliando animais taurinos.

Olivieri et al.[12], avaliando bovinos Nelore, encontraram genes localizados em regiões relacionadas à EA que codificam proteína de ligação à guanosina trifosfato (GTP), e estão associados a ligação de íons de cálcio, regulação de tráfego de membrana, à atividade nos canais cálcio/potássio, resposta ao stress metabólico, processos de troca iônica, regulação do pH, eliminação dos ácidos produzidos pelo próprio metabolismo do organismo, e ao

metabolismo de carboidrato. Para CAR, Olivieri et al.[12] encontraram genes que desempenham funções relacionadas ao metabolismo de insulina, receptores olfativos, transporte de íons, sistema imune, canais de cálcio. Para CMS, Olivieri et al.[12] relataram genes associados ao transporte de íons, paladar e receptores olfativos.

As diferentes vias metabólicas já relatadas associadas à eficiência alimentar reforçam a natureza complexa dessas características e os mecanismos envolvidos na expressão fenotípica e na identificação de animais mais eficientes quanto ao uso de alimento[33]. Ainda assim, as análises funcionais realizadas com características relacionadas à eficiência alimentar revelaram diversas vias associadas a mecanismos relacionados à produção e gasto de energia e também às exigências de mantença[12,38,40,98,99,100,68,96,69]. Além disso, é importante ressaltar que a maioria dos bancos de dados e das ferramentas disponíveis para realização de analises funcionais e de vias metabólicas são referentes a estudos com características relacionadas a doença e com seres humanos, como a ampla gama de estudos com ontologia humana, sendo essa uma limitação para estudos com características produtivas e espécies animais. Outra limitação é que a maioria dos estudos visam animais taurinos e que os bancos de dados disponíveis, assim como os genomas de referências estão em constante atualização. Assim e apesar dessas informações serem valiosas, ainda são insuficientes para elucidar todos os mecanismos que afetam a expressão fenotípica da eficiência alimentar[27]. A identificação desses mecanismos pode ser utilizada para melhor compreensão biológica das características associadas à eficiência alimentar, uma vez que indicam os processos fisiológicos que afetam a variância genética e sua manifestação no fenótipo e, assim, fornecem conhecimento sobre os componentes genéticos dessas características.

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CAPÍTULO 2 - Selection criteria for feed efficiency related traits and its association with growth, reproductive and carcass traits in Nelore cattle

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Selection criteria for feed efficiency traits

Abstract

Context: Livestock feed costs have a high impact on the profitability of beef production systems and is directly related to feed efficiency. However, these traits show high costs and hard to measure, reducing the availability of phenotypic records and reliability of genetic evaluations. Thus, the use of genomic information can increase the robustness of genetic studies that address them.

Aims: The aim of this study was to estimate genetic parameters for feed efficiency, growth, reproductive and carcass traits in Nelore cattle and the correlated response among them, using genomic information. The direct and correlated response for feed efficiency related traits were also estimated.

Methods: Residual feed intake (RFI), dry matter intake (DMI), feed conversion ratio (FCR), feed efficiency (FE), residual average daily gain (RG), residual intake and average daily gain (RIG), birth weight, weight at 120, 240, 365 (W365), and 450 days of age, scrotal circumference at 365 and 450 days of age, rib eye area (REA), backfat thickness and rump fat thickness were evaluated. The genetic parameters were estimated using the single-step genomic BLUP approach (ssGBLUP).

Key results: The feed efficiency related traits showed low to moderate heritabilities, ranging from 0.07 to 0.23. Feed efficiency related traits showed low genetic correlations with reproductive (-0.24 to 0.27), carcass (-0.17 to 0.27) and growth (-0.19 to 0.24) traits, except for growth with DMI (0.32 to 0.56) and W365 with FE (-0.40). The direct selection for higher W365 would result in reducing FE and increasing FCR, and direct selection for higher REA would result in an increasing FCR.

Conclusions: The selection to improve growth, reproductive and carcass traits would not change RFI, RG, and RIG. The choice of the most adequate selection criterion depends on the production system, i.e. RFI might be indicated for low input beef cattle systems, still RIG would be more appropriate for more intensive and without any dietary restrictions beef cattle systems. **Implications:** The estimates of heritability and genetic correlations suggest that genetic selection for feed efficiency using RFI, RG and RIG in Nelore cattle lead to higher genetic gain than FE and FCR, without affecting other profitability traits.

Key-words: *Bos indicus,* genetic correlation, residual average daily gain, residual feed intake, single step Genomic Best Linear Unbiased Prediction

Introduction

Livestock feed costs have been pointed as the main component of total costs in animal protein production systems, and there is a growing concern, in the last years, about the beef cattle operation costs, which can reduce the beef cattle profitability (Boaitey *et al.* 2017). In this context the selection of animals for higher feed conversion efficiency reduces the use of natural resources, loss of energy consumed, greenhouse gas emissions and manure production (Ferrell and Jenkins 1985; Arthur and Herd 2008; Boaitey *et al*. 2017).

The residual feed intake (RFI), residual average daily gain (RG) and residual intake and average daily gain (RIG) are weakly associated with growth traits (Koch *et al.* 1963; Berry and Crowley 2012). So, selection based on RFI, RG and RIG lead to more efficient animals and may not change the adult size or weight gain (Koch *et al.* 1963; Basarab *et al.* 2003; Crowley *et al.* 2010; Berry and Crowley 2012; Grion *et al.* 2014). In addition, studies working mainly with taurine breeds concluded that the selection for RFI, RG, and RIG would not influence the carcass, reproductive and weight gain composition traits (Koch *et al*. 1963; Arthur and Herd, 2008; Crowley *et al.* 2010; Berry and Crowley 2012, 2013; Torres-Vázquez *et al.* 2018).

Several studies pointed out that there is genetic variability and moderate heritability estimates for RFI, RG, and RIG in Zebu breeds (Koch *et al.* 1963; Crowley *et al*. 2010; Berry and Crowley 2012; Grion *et al*. 2014; Santana *et al*. 2014).

Although the economic and environmental importance of feed efficiency related traits, these traits have been little used as a selection criterion in Zebu breeding programs due to the high costs and hard to measure, reducing the availability of phenotypic records and reliability of genetic evaluations. Most of the studies for feed efficiency with Zebu breeds were performed with experimental populations or in few commercial herds with small sample size (de Oliveira *et al.* 2014; Grion *et al.* 2014; Santana *et al.* 2014; Ceacero *et al.* 2016; Olivieri *et al.* 2016). Moreover, few studies with small sample size have quantified the genetic relationship between feed efficiency related traits with growth, reproductive and carcass traits in beef cattle (Grion *et al*. 2014; Santana *et al.* 2014; Ceacero *et al*. 2016; de Moraes *et al.* 2017; Polizel *et al.* 2018; Bonamy *et al.* 2019; Moraes *et al.* 2019). Additional studies with larger sample size under different conditions and including genomic information are necessary in order to increase the reliability and consistence of genetic parameters. Thus, additionally with larger sample size, the inclusion of genomic information and higher number of records could improve the reliability and robustness of breeding value predictions and genetic parameter estimates (Boddhireddy *et al.* 2014). This information is fundamental for the adoption of feed efficiency related traits as a large-scale selection criterion in beef cattle production systems.

The aim of this study was to estimate genetic parameters for feed efficiency, growth, reproductive and carcass traits in commercial Nelore cattle herds, using the single step genomic best linear unbiased prediction (ssGBLUP) method. In addition, the direct and correlated response for feed efficiency related traits when direct selection was applied for growth, reproductive and carcass traits were estimated.

Material and Methods

Ethics statement of animal experimentation

The research project was approved by the Committee on Ethics in the Use of Animals (CEUA/PRPI) of Universidade Federal de Goiás (UFG), according to protocol N° 088/18 issued by this institution.

General information about the data

Records for growth, reproductive and carcass traits from 15,639 Nelore animals (13,219 males and 2,510 females) born between 2010 to 2017, calves of 766 sires and 10,056 dams, were considered and provided by the Nelore Brazil Breeding Program, coordinated by the National Association of Breeders and Researchers (ANCP). Data from 4,329 animals (3,150 males and 1,179 females) tested for feed efficiency, carried out between 2011 and 2018, and genotypic information for 3,594 animals (2,762 males and 832 females born between 2010 to 2017) were considered. The relationship matrix A was calculated based on pedigree information from 58,374 animals with 6,309 sires and 37,147 dams through nine generations. The animals that composed the data set had an average inbreeding of 0.071%, and the proportion of inbred individuals was 0.41% over the total population. These parameters were estimated using the INBUPGF90 program (Ignancy Misztal and collaborators; University of Georgia, Athens, GA, USA).

DNA samples were obtained from hair follicles. The animals were genotyped for SNPs markers using CLARIFIDE® Nelore 3.1 low-density panel, containing approximately 29,000 SNP markers. DNA extraction and sample genotyping were performed by Zoetis® (Kalamazoo, MI), through its protocol. In the quality control (QC) for genomic data, SNPs with minor allele frequency (MAF), call rate and p-value for Hardy-Weinberg equilibrium test (HWE) less than 0.02; 0.95 and 0.15, respectively, were excluded. Only SNPs in autosome chromosomes and

with known position according to UMD 3.1 bovine genome were considered. Samples with call rates below to 0.95 were excluded from the analysis. This process was performed with R 4.0.2 (R Development Core Team, Vienna, Austria), using scripts developed for this purpose, resulting in a data set with 19,602 SNP and 3,467 animals.

Feed efficiency traits

A total of 125 feed efficiency tests were performed to assess the feed efficiency related traits. The animals were evaluated in feedlot under similar management and environmental conditions, using the same protocol (Mendes *et al*. 2020) in three farms (HoRa Hofig Ramos, Rancho da Matinha and AgroNova) and two research centers (Embrapa Rice and Beans and Federal University of Uberlandia). Even though the diets offered over the years differed in composition and ingredients, they were formulated based on silage and commercial concentrate, with an average of 64% total digestible nutrients, 13% crude protein, 76% dry matter and formulated (Mendes *et al.* 2020). The amount offered was enough to allow refuse between 5% and 10% of the total offered. During the tests, the individual average weight was obtained every 14 days. Forage, concentrate and wastes samples were collected every week to evaluate chemical composition. The feed efficiency related traits were estimated within the feed efficiency test group.

The DMI was measured by collective stalls equipped with automated systems (GrowSafeSystem® and Intergado®), for a minimum of 70 days preceded by adaptation. The DMI was calculated as the amount of individually consumed feed automatically recorded by the electronic systems (GrowSafeSystem® and Intergado®) The DMI, measured in kg/day, was obtained by calculating the average of all daily intake values during the test period. As quality control, daily DMI records within ± 3.5 standard deviations from the average daily DMI of the test group were considered in the analysis. Additionally, daily DMI obtained on days with a

power outage or weighing scale adjustments were excluded from the analysis (Mendes *et al.* 2020).

To estimate RFI and RG, average daily gain (ADG) and metabolic body weight ($MW^{0.75}$) were calculated. ADG (kg/day) was estimated by the linear regression coefficient of the weights as a function of the days in test (DIT), using the *lm* function of R 4.0.2 (R Development Core Team) and the following equation:

$$y_{ij} = \alpha_i + \beta_i * DIT_j + \varepsilon_{ij}$$

where y_{ij} is the j[th] observation of weight of i[th] animal; α_i is the intercept of the regression equation which represents the initial weight of animal I; β_i is the linear regression coefficient which represents the ADG; DIT_j is the day in the performance test of the j[th] observation, and ε_{ij} is the residual associated to each observation. It was assumed that the residues were independent and not correlated and residual effects were normally distributed with mean zero. The $MW^{0.75}$ was given from initial body weight and ADG:

$$MW_i^{0.75} = \left[\alpha_i + \beta_i * \left(\frac{DIT_j}{2}\right)\right]^{0.75}$$

where $MW_i^{0.75}$ is the metabolic weight of i[th] animal; α_i is the intercept of the regression equation which represents the initial weight of i[th] animal; β_i is the linear regression coefficient which represents the ADG, as described and obtained above in estimating ADG.

Feed efficiency (FE), measured in kg ADG/kg DMI, was obtained as the ratio between ADG and DMI and the highest values are desirable. Feed conversion ratio (FCR), measured in kg DMI/kg ADG, was obtained by the inverse ratio (DMI/ADG) and lower values are desirable. RFI (kg/day) was estimated, within each contemporary group (CG), by the residual of the DMI regression as a function of ADG and $MW^{0.75}$, using the R 4.0.2 (R Development Core Team) and the equation (Koch *et al.* 1963):

$$y_i = \beta_o + \beta_1 ADG + \beta_2 MW_i^{0.75} + \varepsilon_{ij}\ (RFI)$$

where y_i is individual dry matter intake of i[th] animal; β_o is the intercept; β_1, and β_2 are the linear regression coefficient of ADG and $MV_i^{0.75}$, respectively; and ε_{ij} is the residual error, i.e. RFI. It was assumed that the residues were independent and not correlated and residual effects were normally distributed with mean zero (Sen and Sen 2014). Regression analysis was performed and no effect of backfat thickness (BF) on RFI was observed, thus the RFI was not adjusted for fat thickness.

The RG (Koch *et al.* 1963; Berry and Crowley 2012) (kg of ADG/day) was obtained as the difference between the observed ADG and the estimated based on DMI and $MW^{0.75}$. The estimated average daily gain ($ADGE_i$) was obtained using the *lm* function on the R 4.0.2 (R Development Core Team), within CG and by:

$$ADGE_i = \beta_o + \beta_1 DMI + \beta_2 MW_i^{0.75} + \varepsilon_{ij} \ (RG)$$

where β_0 is the intercept, β_1, and β_2 are the regression coefficients of DMI and $MW_i^{0.75}$, respectively; and ε_{ij} is the residual error, i.e. RG. It was assumed that the residues were independent and not correlated and residual effects were normally distributed with mean zero (Sen and Sen 2014).

RIG was calculated as the difference between RG and RFI, after standardize both traits to a variance of 1, allowing the combination into a single value (Berry and Crowley 2012). Both traits, RFI and RG, are linear functions of their component traits: DMI, ADG, and $MW^{0.75}$. Animals with negative RFI consume less than expected and are deemed more efficient, and animals with positive RG and RIG grow more rapidly than is expected and are thus deemed more efficient (Berry and Crowley 2012).

Performance traits, statistical and quality control analyses

The analyzed growth traits were birth weight (BW), adjusted weight at 120 (W120), 240 (W240), 365 (W365) and 450 (W450) days of age. The live weight was measured every 90

189 days up to 18 months of age. Adjusted weight was calculated using the formula proposed by
190 Garnero *et al.* (2001), in which the average daily gain (kg/day) of each period, is used to adjust
191 a standard age.

192 Reproductive traits analyzed were scrotal circumference adjusted at 365 (SC365) and
193 450 days (SC450). The scrotal circumference was measured every 90 days from nine up to 18
194 months, using a specific metric tape for this purpose.

195 Carcass traits were obtained by ultrasound evaluation (Aloka 500 SSD with transducer
196 3,5 MHz) as described by BIF (2002). Rib eye area (REA, evaluated in cm^2) and BF (measured
197 in millimeters, mm) were measured between the 12^{th} and 13^{th} ribs in the *Longissimus Dorsi*
198 muscle. The rump fat thickness (RF) (obtained in millimeters, mm) was measured at the
199 intersection of the *Gluteus Medius* and *Biceps Femoris* muscles, which is located between ileum
200 and ischium bones.

201 For growth and carcass traits, the CG was composed by farm/instituition, management
202 group, sex, year and birth season (dry season from April to September and the rainy season
203 from October to March). The same CG composition was used for SC with except sex. The
204 groups formed to assess feed efficiency were composed of farm, management group, sex, year
205 and birth season, with a range of 90 days of age. Therefore, for feed efficiency related traits,
206 the CG was composed by feed efficiency test. Records within ± 3.5 standard deviations from
207 the CG mean and CG that had at least four animals were considered in the analysis. The number
208 of records and descriptive statistics for the traits are summarized in Table 1.

209

210 *Estimation of variance components*

211 The (co)variance components and genetic parameters were estimated considering the linear
212 animal model and ssGBLUP (Aguilar *et al.* 2010), in single- and two-trait analyses. These

analyses were performed using the restricted maximum likelihood method, with REMLF90 and AIREMLF90 software (Ignancy Misztal and collaborators).

The estimates obtained by REMLF90 were used as starting values for AIREMLF90 software (Average-Information algorithm). The AIREMLF90 software estimated the standard-error (SE) values of the covariances components and heritabilities. The SE was calculated by the program with a function of covariances using repeated samplings of parameters estimates from their asymptotic multivariate normal distribution (Meyer and Houle 2013).

For BW, W120 and W240, the direct additive genetic, maternal additive genetic, maternal permanent environment, and the residual effect as random effect, and the fixed effects of CG and cow's age at calving as covariate (linear and quadratic effect) were included in the model. For W365, W450, SC365 and SC450 the direct additive genetic, and the residual effect as random effect, and the fixed effects of CG were included in the model. For carcass and feed efficiency traits, the direct additive genetic, the residual effect as random effect, and the fixed effects of CG and animal's age as covariate (linear effect) were included in the model. The animal model equation used was:

$$y = X\beta + Z_1 a + Z_2 m + Z_3 mpe + e$$

where y is the vector of the phenotypes; X is the incidence matrix associating β with y; β is the vector of fixed effects, including the CG, the dam's age at calving (BW, W120 and W240) and animal's age (carcass and feed efficiency related traits); Z_1 is the incidence matrix associating a with y; a is the vector of random direct additive genetic effects; Z_2 is the incidence matrix associating m with y, only for BW, W120 and W240; m is a vector of maternal additive genetic effects; Z_3 are the incidence matrix associating mpe with y, only for BW, W120 and W240; mpe is a vector of maternal permanent environment effects; and e is the vector of residual random effects. It was assumed that $\mathrm{E}[\mathbf{y}] = \mathbf{X\beta}$; with the direct additive genetic, additive maternal, maternal permanent environment and residual effects assumed normally distributed

with mean zero and $\mathrm{Var}(\boldsymbol{a}) = \mathbf{H} \otimes \mathbf{S}_{\mathrm{a}}$, $\mathrm{Var}(\boldsymbol{m}) = \mathbf{I} \otimes \mathbf{S}_{\mathrm{m}}$, $\mathrm{Var}(\boldsymbol{mpe}) = \mathbf{I} \otimes \mathbf{S}_{\mathrm{mpe}}$ and $\mathrm{Var}(\mathbf{e}) = \mathbf{I} \otimes \mathbf{S}_{\mathrm{e}}$; in which $\mathbf{S}_{\mathrm{a}}$, $\mathbf{S}_{\mathrm{m}}$, $\mathbf{S}_{\mathrm{mpe}}$ and $\mathbf{S}_{e}$ is the additive genetic, additive maternal, maternal permanent environmental and residual covariance matrix, respectively, and $\mathbf{I}$ is an identity matrix of appropriate order.

The ssGBLUP method is a modification from the traditional best linear unbiased prediction (BLUP), in which the relationship matrix numerator A^{-1} is replaced by H^{-1} (Aguilar *et al.* 2010), combining pedigree and genomic information:

$$H^{-1} = A^{-1} + \begin{bmatrix} 0 & 0 \\ 0 & G^{-1} - A_{22}^{-1} \end{bmatrix}$$

where H is the relationship coefficients matrix between the animals; G is the genomic relationship matrix; A is the additive relationship matrix; and A_{22} is a subset of the additive relationship matrix for the genotyped animals. The genomic matrix (G) was created as follows (VanRaden 2008):

$$G = \frac{ZDZ'}{\sum_{i=1}^{M} 2p_i(1-p_i)}$$

Where, Z is an incidence matrix adjusted for allele frequencies; D is a diagonal matrix of weights for SNP variances; M is the number of markers, and p_i represented the minor allele frequency of the i$^{\text{th}}$ SNP. These factors were obtained ensuring that the average diagonal in G is close to that of A_{22}. After estimating the variance components, the heritability and genetic and phenotypic correlations were calculated. The significance of the correlation estimates was verified through hypothesis test (Lira and Neto 2006), considering as a threshold the p-value 0.05.

Response to selection

The expected response to direct selection was estimated using the following equation (Falconer and Mackay 1996):

$$\Delta G_Y = r_{tiY} * i_Y * \sigma_{aY}$$

where, ΔG_Y is the genetic gain in trait *Y* per generation; r_{tiY} is the accuracy of genetic prediction of *Y*, obtained as square root of heritability; i_Y is the intensity of selection for trait *Y*; and σ_{aY} is the genetic variation, obtained as standard deviations (SD) of the additive genetic effect in trait *Y*. To define the selection intensity, the proportion of the data set with phenotype records was considered, where growth and carcass traits displayed higher proportion of phenotyped animals and higher selection intensity, since these traits are assessed in both sexes and are easy and cheap to measure, compared to efficiency traits (also recorded in both sexes). Based on these considerations, the selection intensity assumed for growth, reproduction, carcass, and feed efficiency related traits were 1.76 (selection of 4% males and 45% females), 1.40 (selection of 5% males and 40% females), 1.76 (selection of 4% males and 45% females) and 0.97 (selection of 15% males and 70% females), respectively.

Correlated responses for feed efficiency related traits when direct selection was applied for growth, carcass and reproductive traits, were estimated by the following equation (Falconer and Mackay 1996):

$$\Delta G_{Y|X} = r_{gXY} * r_{tiX} * i_X * \sigma_{aY}$$

where, $\Delta G_{Y|X}$ is the genetic gain per generation in trait *Y* (feed efficiency related traits), given selection for *X* (growth, reproductive and carcass traits); r_{gXY} is the genetic correlation between *X* with *Y*; r_{tiX} is the accuracy of genetic prediction of *X;* i_X is the intensity of selection for trait *X*; and σ_{aY} is the SD of the additive genetic effect on trait *Y*.

The relative efficiency of selection (RES) was calculated as the ratio between the direct and indirect response to the selection, as below:

$$RES = \Delta G_Y / \Delta G_{Y|X} * 100$$

For *RES* values below 100% (or between -1 to -100%), the genetic gain for *Y* trait is expected to be higher if the direct selection is made for *X* trait (indicator trait). On the other

hand, for *RES* values above 100% (or below -100%), it is expected that the genetic gain for the *Y* trait is higher if the selection is made directly for it, than direct selection for other traits. RES values equal to 100%, indicate that direct selection for *Y* trait or direct selection for *X* trait may result in the same genetic gain for *Y* trait. For the direction and response to selection, negative values indicate that the response is inversely proportional, i.e. the direct selection for increase in *X* traits leads to a reduction in *Y* trait. Conversely, positive values of the relative efficiency of selection indicate that the selection to increase *X* trait also increases *Y* trait.

Results

The direct heritability estimates for growth traits were of moderate magnitude (Table 2). Direct heritabilities for feed efficiency related traits were low to moderate, with values of 0.07, 0.09, 0.17, 0.17, 0.20, 0.23 for FE, FCR, RFI, RG, RIG and DMI, respectively.

The genetic and phenotypic correlation estimates between feed efficiency related traits are shown in Table 3. Genetic correlations between RFI with DMI (0.76) and FCR (0.45) were positive and moderate; and between RFI with FE (-0.54), RG (-0.23) and RIG (-0.61) were negative and low to moderate. Genetic correlations between DMI with FE (-0.50), RG (-0.13), and RIG (-0.62) were negative and low to moderate; and between DMI with FCR (0.32) were positive and moderate. Genetic correlation between FE with FCR (-0.46) was negative and moderate, and between FE with RG (0.28) and RIG (0.54) was positive and moderate. The genetic correlations between FCR with RG (-0.58) and RIG (-0.55) were negative and moderate. The genetic correlation estimated between RG with RIG was moderate (0.46). The phenotypic correlation between RG with RIG (0.35) were moderate.

Estimates of genetic and phenotypic correlations between feed efficiency related traits with growth, reproductive and carcass traits are presented in tables 4, 5 and 6, respectively. The SD values obtained for the genetic and phenotypic correlations were low.

Genetic correlations between DMI with BW (0.23) were low; and moderate between DMI with W120 (0.32), W240 (0.36), W365 (0.56), W450 (0.56). The genetic correlation between growth traits with RFI (-0.02 to 0.22), FE (-0.19 to -0.07), FCR (0.08 to 0.24), RG (-0.15 to 0.17) and RIG (-0.16 to 0.08) were low, with the exception between FE with W365 (-0.40). In addition, genetic correlations between BW with RFI (-0.02) and RIG (0.03) were non-significant (NS). Overall, phenotypic correlations between feed efficiency with growth traits were low, except between W450 with FE (-0.43). Phenotypic correlations between RFI with growth traits (-0.02 to 0.04), and RIG with BW (-0.03), W120 (-0.04), and W450 (0.02) were NS.

The genetic correlations estimates between SC365 and SC450 with RFI (0.17 and 0.19), DMI (0.25 and 0.27), FCR (0.16 and 0.10), RG (0.06 and 0.08) and RIG (0.21 and 0.24) were positive and low. For SC365 and SC450 with FE (-0.17 and -0.11) were negative and low. Phenotypic correlations between feed efficiency related traits with scrotal circumference were low, varying from -0.23 to 0.24. Also, phenotypic correlations between RFI with SC (0.01 to 0.04), and SC450 with RIG (-0.02) and RG (-0.05) were NS.

Genetic correlation estimates between carcass traits with RFI (0.04 to 0.13), DMI (-0.05 to 0.15), FE (-0.17 to -0.04), FCR (0.02 to 0.27), RG (-0.12 to 0.05), and RIG (-0.02 to 0.07) were low. Genetic correlations between REA with RFI (0.04) and RIG (-0.02), and BF with FE (-0.04), and FCR (0.02) were NS. Overall, the phenotypic correlations between feed efficiency with carcass were low. Phenotypic correlations between REA with RFI (-0.03), FCR (0.04), and RG (-0.01), BF with RFI (-0.02), FE (-0.04), RG (0.03) and RIG (-0.02), and RF with RFI (0.02), FE (-0.03), RG (0.03) and RIG (-0.03) were NS.

The relative efficiency of selection for feed efficiency related traits are shown in Table 7, being the ratio of genetic gain obtained in *Y* trait (second line), in response to direct selection for *X* trait (indicator trait - first column). Direct selection for RFI (-297.52, 314.86 and -

448.23%, respectively) and DMI (-373.74, 515.02 and -922.41%, respectively) may result in higher genetic gain than indirect genetic gains by direct selection for FE, FCR and RG. For RIG, direct selection may result in lower genetic gain than indirect genetic gain by direct selection using RFI, DMI and RG (-83.31, -95.06 and 93.09%, respectively).

The relative efficiencies of selection for feed efficiency related traits when direct selection were performed for growth, reproductive and carcass traits in Nelore cattle are shown in Table 8, being the ratio of genetic gain obtained in *Y* trait (second line), in response to direct selection for *X* trait (indicator trait - first column). For RFI, RG, and RIG, direct selection may result in higher genetic gains than indirect gains by selection using growth, reproductive or carcass traits. For DMI, a higher indirect response was observed through direct selection for W365 and W450 (84.70 and 87.39%, respectively). The direct selection for higher W365 would result in a higher indirect response in FE (-65.42%) and FCR (93.63%), than selection directly for these traits. Direct selection for REA would also be more effective in obtaining indirect genetic gains for FCR (98.27%), than direct selection for itself.

Discussion

Direct selection for maternal effects has been difficult, since the estimated genetic value (EBV) for maternal weaning weight is expressed in the weaning weight of bull's grand progeny (Kluskaa *et al*. 2018). However, an important proportion of phenotypic variance for pre-weaning weights was due to maternal and maternal permanent environmental effects. Thus, the inclusion of these effects in the model used to estimate genetic parameters has importance to obtain reliable estimates. The results obtained in this study are similar to several reports evaluating Nelore cattle (Lopes *et al.* 2016; Pires *et al.* 2017; Kluskaa *et al.* 2018).

The heritability estimates for growth traits obtained in this study were moderate in accordance with several reports for Nelore cattle (Yokoo *et al.* 2010; Zuin *et al.* 2012; Grion

362 *et al.* 2014; Lopes *et al.* 2016; Pires *et al.* 2017; Bonamy *et al.* 2019), whose estimates range
363 from 0.27 to 0.30 (BW); 0.22 to 0.26 (W120); 0.22 to 0.29 (weaning weight); 0.29 to 0.33
364 (W365); 0.31 to 0.55 (W450). For scrotal circumference, heritability estimates were higher and
365 similar to those reported for beef cattle, with values ranging from 0.29 to 0.48 for SC365 and
366 0.42 to 0.51 for SC450 (Arthur *et al.* 2001; Yokoo *et al.* 2010; Pires *et al.* 2017; Kluskaa *et al.*
367 2018; Bonamy *et al.* 2019). Heritability estimates obtained for REA, BF, and RF were lower
368 than those reported by de Moraes *et al.* (2017) (0.45 to 0.51) and Yokoo *et al.* (2010) (0.29 to
369 0.50); but similar to the estimates reported by Santana *et al.* (2014) (0.20 to 0.38) and Bonamy
370 *et al.* (2019) (0.21 to 0.34). All cited studies were performed evaluating Nelore cattle.
371 For RFI, the heritability estimated was within the range presented in the literature for
372 beef cattle (0.13 to 0.28) (Grion *et al.* 2014; Oliveira *et al.* 2014; Olivieri *et al.* 2016; Silva *et*
373 *al.* 2016). The moderate heritability estimates for DMI were also reported by Oliveira *et al.*
374 (2014) (0.29) and de Moraes *et al.* (2017) (0.25 to 0.36), in Nelore cattle. Heritability estimates
375 obtained for RG and RIG were within the range reported in the literature for Nelore cattle,
376 which range from 0.11 to 0.36 (Berry and Crowley 2012; Grion *et al.* 2014; Ceacero *et al.*
377 2016). The residuals for RFI, RG, and RIG included, in addition to the variation that is not
378 captured by the independent variables used in the equation, the random measurement errors of
379 DMI and ADG (de Moraes *et al.* 2017); rather than the separate measurement error of each
380 variable as DMI and growth traits. This conclusion can lead to lower estimates of additive
381 variance and heritability for these traits.
382 The heritability estimates for FE and FCR observed in this study were lower than the
383 estimates presented in the literature, which range from 0.13 to 0.17 for FE and 0.11 to 0.19 for
384 FCR (Grion *et al.* 2014; Ceacero *et al.* 2016; Olivieri *et al.* 2016; Silva *et al.* 2016; Polizel *et*
385 *al.* 2018). Lower heritability estimates for FE and FCR may be attributed to a large part of the
386 genetic variation for these traits is due to genetic differences in DMI and ADG between animals

(Ceacero *et al.* 2016). These traits were obtained by the ratio between DMI and ADG and selection through this ratio is less efficient than using linear indices, since traits obtained as a ratio have the potential to cause bias in breeding value prediction (Gunsett 1984; Arthur *et al.* 2001; Berry and Crowley 2013). Thus, FE and FCR have a disadvantage compared to indices traits such as RFI, RG, and RIG.

Since the RFI is a function of intake, the genetic correlation between RFI with DMI was moderate and within a range of estimates reported by several authors for Nelore cattle (0.33 to 0.95) (Grion *et al.* 2014; Santana *et al*. 2014; Ceacero *et al.* 2016; de Moraes *et al.* 2017; Polizel *et al*. 2018). These results confirm that the selection for lower RFI would reduce the feed intake. Considering the relative efficiency of selection obtained, it is expected that the response to selection in RFI would be higher due to the direct selection for DMI. This result can be attributed to moderate genetic correlations between these traits and the higher heritability estimates for DMI than RFI.

The positive and moderate genetic correlation between RFI with FCR was similar to the estimates reported by Polizel *et al.* (2018) (0.50) and Santana *et al.* (2014) (0.49), in Nelore cattle. Despite the moderate genetic correlation between RFI with FE and FCR, the relative efficiency obtained shows that the selection for FE and FCR would result in lower genetic gain than direct selection for RFI. The low heritability and accuracy for FE and FCR support these results.

Negative and moderate genetic correlations between RFI with RG and RIG were also reported by Santana *et al.* (2014) (-0.56 to -0.34) in Nelore cattle. A negative estimate, but, of lower magnitude than those displayed in this study, was reported by Crowley *et al.* (2010) (-0.46) between RFI with RG in taurine bulls. The moderate genetic correlations between RFI with RG and RIG were expected, considering the interrelationship between them, since they are all associated with weight gain, reflecting the lower intake compared to weight gain or vice

412 versa (Berry and Crowley 2012). However, RG has been proposed as an alternative for selection
413 of more efficient animals, being dependent of live weight gain. On the other hand, RFI is
414 independent of live weight gain, that can be one of the reasons for the low adoption of this trait
415 in beef cattle breeding programs, since slow-growing animals can be considered efficient when
416 presenting negative RFI (Berry and Crowley 2012). Similar problem can be attributed to RG
417 when DMI is evaluated (Berry and Crowley 2012; Ceacero *et al.* 2016). Thus, the combination
418 of RFI with RG in RIG ensures independence of adult size and a desirable relationship with
419 DMI and ADG (Berry and Crowley 2012; Ceacero *et al.* 2016). Considering the higher genetic
420 correlation between RFI with RIG than RG, is expected that indirect response in RFI due to
421 direct selection for RIG would be more effective than direct selection for RFI. These results are
422 also attributed to the higher heritability and prediction accuracy of RIG than RFI. On the other
423 hand, considering RG as a selection criterion, it is expected that direct selection for RFI will
424 result in higher genetic gains since RG and RFI have similar heritability estimates.

425 Moderate phenotypic correlations between RFI with DMI demonstrated that RFI could
426 be an indicator of animals with lower feed intake. The negative and moderate phenotypic
427 correlation between RFI and RIG indicated that reduction of RFI could lead to an increase in
428 RIG, an expected result considering that the first trait is used to obtain the second.

429 The negative and moderate genetic correlation between DMI with RIG is within the
430 range reported in several reports (-0.87 to -0.29) (Berry and Crowley 2012; Grion *et al.* 2014;
431 Santana *et al.* 2014; Ceacero *et al.* 2016). These estimates demonstrate the feasibility of using
432 RIG for selection to reduce DMI, confirmed by the higher efficiency of selection in DMI
433 obtained with the direct selection for RIG. Considering these estimates, it is expected that direct
434 genetic selection to reduce DMI would result in higher genetic gain than selection for RG.
435 Negative and low genetic correlations between DMI with RG was similar to those reported by

436 Santana *et al.* (2014) (-0.12) evaluating Nelore cattle; and Crowley *et al.* (2010) (-0.03) for
437 taurine breeds.

438 Positive and moderate genetic correlation between DMI with FCR obtained in this study
439 was within the range reported for Nelore cattle (0.10 to 0.60) (Santana *et al.* 2014; Polizel *et al.*
440 2018). The direct selection for FCR would result in a lower genetic gain for DMI than selecting
441 for itself, which is due to the correlation between DMI with FCR and the low heritability of the
442 last trait. Despite the moderate genetic correlation between these traits, a low indirect response
443 in the DMI is expected from the direct selection for FE, due to the low heritability for FE.
444 Therefore, selection to improve FE or reduce FCR will change feed intake given the genetic
445 correlation (Table 3), but the magnitude of this change is expected to be low, and direct
446 selection for DMI is recommended to reduce feed intake rather than selection for FE and FCR.
447 The negative and moderate phenotypic correlation between DMI with FE and RIG demonstrates
448 that these traits may be a phenotypic indicator of lower intake animals.

449 The moderate and negative genetic correlation between FE with FCR is because these
450 traits were obtained from the same inverse ratio. Although the genetic correlations between FE
451 with FCR, RG and RIG were moderate, is expected low relative efficiency of selection obtained
452 using FE as a selection criterion. The low FE heritability estimated can lead to low indirect
453 gain. The moderate phenotypic correlation between FE with FCR (negative), RG and RIG
454 (positive) indicated that animals that show higher feeding efficiency would also be those with
455 lower feed conversion and higher residual average daily gain.

456 The negative and moderate genetic correlation between FCR with RIG was similar to
457 that presented by Santana *et al.* (2014) (-0.48), in Nelore cattle. Higher genetic correlation
458 between FCR with RG was reported by Torres-Vázquez *et al.* (2018) (-0.92) in Angus cattle
459 and by Crowley *et al.* (2010) (-0.89) in beef bulls. Despite the moderate correlation between
460 RG and RIG with FCR, the genetic gain for RG and RIG would be higher with the direct

461 selection for this trait than selection for FCR. The higher heritability and additive genetic effect
462 for RIG and RG support these results. Considering the negative and moderate phenotypic
463 correlation between FCR with RG, is expected that animals with lower feed conversion showed
464 higher residual average daily gain.

465 The RIG is obtained by combining the RFI and RG and, thus, it was expected moderate
466 genetic correlation, such as observed in this study. Higher estimates were reported by Berry and
467 Crowley (2012) for genetic correlation (0.83) between RIG with RG. The moderate genetic
468 correlation between these traits indicated that the selection for RG would result in a higher
469 indirect genetic gain in RIG than direct selection for itself. The moderate phenotypic correlation
470 between RG with RIG is expected and indicates that RG is a good phenotypic indicator of RIG
471 and vice versa.

472 The highest genetic correlation estimates between DMI with growth traits were obtained
473 for W365 and W450, which are measured in the same age of the feed efficiency test and
474 indicated that the selection for the heavier animals would lead to higher intake animals (Arthur
475 *et al.* 2001). This result is attributed to moderate genetic correlation and the highest prediction
476 accuracy (obtained as the square root of heritability) of W365, and W450. The increase in DMI
477 is not desired, due to the increased feedstuffs costs and because it may not lead to obtaining
478 more efficient animals. Similar genetic correlations were reported by Arthur *et al.* (2001) (0.28-
479 0.56) and Torres-Vázquez *et al.* (2018) (0.42-0.68) evaluating Angus cattle, and by Grion *et al.*
480 (2014) evaluating Nelore cattle (0.42).

481 Since RFI is obtained using regression equations composed by ADG and $MW^{0.75}$, is
482 expected that this trait to be phenotypically independent of growth traits (Arthur *et al.* 2001;
483 Berry and Crowley 2012). This pattern corroborates with phenotypic correlations obtained in
484 this study, reinforcing the independence of RFI in weight and adult size (Berry and Crowley
485 2012). Low genetic correlations between RFI with growth traits were obtained. Thus, the

incorporation of weight in RFI regression may capture part of variation observed in the intake attributed to growth and maintenance (Arthur *et al.* 2001). These results agree with the estimates presented by Grion *et al*. (2014) (-0.36 to -0.12) evaluating Nelore cattle, and by Arthur *et al.* (2001) (-0.26 to 0.22) and Torres-Vázquez *et al.* (2018) (-0.02 to 0.25) in Angus cattle.

Considering the negative and moderate genetic correlation between FE and W365, the genetic selection based on FE may result in heavier animals, and, indirectly, larger adult size, growth rate and maintenance requirement, as also reported (Arthur *et al.* 2001; Polizel *et al.* 2018). With the exception of the genetic correlations between DMI with growth, the highest genetic correlation for growth traits was observed between FE and W365, since this weight is measured at similar ages that feed efficiency.

The low genetic correlations between FCR with growth traits are in agreement with those presented by Nkrumah *et al.* (2007) (0.06 to 0.20) in beef cattle. Low genetic correlation between RG and growth traits are close to those reported by Torres-Vázquez *et al.* (2018) (-0.12 to 0.21), in beef cattle. For RIG and growth traits, the low genetic correlation estimated was expected since the traits used to obtain RIG (RFI and RG) showed low genetic correlation with growth traits. Considering the low phenotypic correlations between FCR, RG and RIG with growth, these traits are poor phenotypic indicators of feed conversion and residual average daily gain.

Although selection for growth affects DMI, it is expected that the response to direct selection for RFI, RG and RIG would be higher than indirect genetic gain obtained with selection for growth traits. The selection for increased W365 would promote a higher negative and positive indirect genetic gain in FE and FCR, respectively, than direct selection for these traits, confirming that the selection for weight is related to the unfavorable reduction of feed efficiency. Low heritability estimates for FE and FCR and the highest genetic correlation of these with W365 than other growth traits support these results. These responses may be

undesirable for the production system because it result in animals with lower feed efficiency or higher feed conversion ratio and heavier weight, which indirectly leads to an increase maintenance requirements (Koch *et al.* 1963; Grion *et al.* 2014).

The direct selection for RFI, DMI, FE, FCR, RG, and RIG would result in higher response than the indirect gains obtained through direct selection for SC. Hence, we find low genetic correlation estimates obtained between feed efficiency related traits with SC. Genetic correlations lower than the observed in this study between SC with DMI (0.21), and RFI (-0.03 to 0.07) was reported in Zebu and other cattle breeds (Arthur *et al.* 2001; Ferreira Júnior *et al.* 2018; Cancino-Baier *et al.* 2019). Low phenotypic correlations between feed efficiency related traits with reproductive traits indicated that SC is poor phenotypic indicator of feed efficiency related traits.

Overall, the low genetic correlations estimates between feed efficiency related traits with carcass traits demonstrate that the genetic selection for animals with higher feed conversion efficiency will not result in major changes in the carcass yield and fat deposition, except for FCR. Indeed, there are other biological mechanisms, besides fat thickness, involved in feed efficiency (Arthur and Herd 2008; Lancaster *et al.* 2009; Santana *et al.* 2014; de Moraes *et al.* 2017), justifying the low estimates obtained. Low genetic correlations between carcass traits with RFI (-0.11 to 0.17), RIG (-0.03 to 0.02), RG (-0.10 to 0.13), FCR (-0.12 to 0.08), and DMI (0.03 to 0.11) were reported in Nelore, Angus, and tropical beef cattle (Arthur *et al.* 2001; Berry and Crowley 2013; Santana *et al.* 2014).

The direct selection for RFI, DMI, FE, RG, and RIG would be more effective than indirect selection using carcass traits. Thus, to obtain animals with higher feed conversion efficiency it is necessary to include feed efficiency related trait as a selection criterion. Despite being low, the genetic correlation between FCR and REA was higher than with other carcass traits. The direct selection for REA has a higher and inversely proportional indirect response in

FCR than the direct response for this trait, due to genetic correlation and lower heritability for FCR.

Despite the RFI, RG and RIG are well known selection criteria to improve feed efficiency and these traits showed similar heritability estimates, the genetic background of these traits are different (Oliveira *et al.* 2014; Olivieri *et al.* 2016; Zhang *et al.* 2020). In this sense, the results of this study showed favorable and low to moderate genetic correlation estimates between these traits, pointed out that the single trait selection for RFI, RG and RIG would lead to different responses in terms of feed efficiency genetic improvement. The choice of the most adequate selection criterion for feed efficiency depends on the production system and breeding objectives. The RFI showed to be a trait that can be an effective genetic selection criterion to reduce feed intake and identify animals with higher feed conversion efficiency, without influencing growth, reproductive, and carcass traits. The use of RFI would be indicated, mainly, for low stocking rate beef cattle and cow-calf operation systems. The RG proved to be a slightly genetically neutral trait in relation to intake and other profitability traits. RIG is more harmonic selection criterion since it allows the identification of animals with lower intake, higher residual average daily gain, and higher feed conversion efficiency. However, the favorable correlated response for DMI would be lower than that obtained for RFI, being RIG more appropriate for more intensive beef cattle systems. FE and FCR might be used in situations without any dietary restrictions and where the objective is a high output, such as feedlot and intensive systems.

It is recommended that selection for feed efficiency related traits be performed through a properly weighted selection index that combines these traits with growth, reproductive and carcass traits, to achieve genetic gain, considering the estimates of correlations and heritabilities obtained and also the productive system objective. Even so, to perform direct selection for feed efficiency related traits is necessary to obtain phenotypic records for these traits.

Feed efficiency related traits are expensive and difficult to measure on an industry-wide basis. Thus, due to the small number of animals used in previous studies, the genetic parameters were estimated with low accuracy (Ceacero *et al.* 2016; Santana *et al*. 2014; Silva *et al.* 2016). So, genomic information is of higher importance in this scenario, since it may be used to improve prediction accuracy, mainly, in genomic selection. This study used a large sample size with animals from different herds spread in different regions of Brazil and evaluated traits that had not been studied extensively in Nelore cattle. Because of the scarce literature reporting genetic parameters for feed efficiency traits using genomic information in Nelore cattle, this study provided estimates that could be useful in the design of breeding programs for improving such traits in this breed. Accordingly, this information may be used for the identification of more efficient animals, attending the market demand, without negative influence in other profitability traits.

Conclusion

The response to selection for residual feed intake, dry matter intake, residual average daily gain, and residual intake and daily gain would be higher than the response obtained for feed efficiency and feed conversion ratio. The selection to improve growth, reproductive and carcass traits would not affect RFI, RG, and RIG in Nelore cattle, so it is possible to improve feed efficiency related traits without affecting the performance in indicine breeds. The feed efficiency and feed conversion ratio could be improve by indirect selection using adjusted weight at 365 days of age as indicator trait.

There is evidence of moderate genetic synergism between the feed efficiency related traits, these traits lead to different responses in terms of feed efficiency genetic improvement. The choice of the most adequate selection criterion for feed efficiency depends on the production system. RFI might be an effective selection criterion to reduce feed intake and

maintenance requirements, being more suitable for low input beef cattle systems. The RIG would allow the identification of lower intake and higher residual body weight gain animals. RIG, FE and FCR would be more appropriate for more intensive and without any dietary restrictions beef cattle systems. However, FE and FCR have a disadvantage compared to RFI, RG, and RIG, since selection for FE and FCR may lead to changes in body weight. In addition, selection to reduce FCR would reduce rib eye area and consequently retail beef cuts.

Conflict of interest statement

The authors declare no conflict of interest.

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Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author upon reasonable request. The data are not publicly available due to privacy or legal restrictions, because it belongs a commercial breeding program.

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Table 1 - Number of records (N), mean, median, standard deviations (SD), coefficient of variation (CV), and number of contemporary groups (N CG) for growth, reproductive, carcass and feed efficiency related traits in Nelore cattle

Traits	N	Mean	Median	SD	CV(%)	N CG
BW (kg)[A]	8864	35.86	36.00	4.61	12.86	101
W120 (kg)[B]	10164	140.94	142.00	20.92	14.84	240
W240 (kg)[C]	8021	216.32	217.00	31.37	14.50	208
W365 (kg)[D]	6613	312.31	313.00	48.83	15.64	113
W450 (kg)[E]	6281	371.75	377.00	58.14	15.64	111
SC365 (cm)[F]	5020	23.32	23.10	2.44	10.48	84
SC455 (cm)[G]	4976	27.54	27.50	3.15	11.42	80
REA (cm^2)[H]	6372	66.65	66.54	8.69	13.04	222
BF (mm)[I]	6366	4.18	3.30	2.71	64.81	222
RF (mm)[J]	6370	5.24	4.57	2.89	55.19	222
RFI (kg/day)[K]	4080	0.00	0.03	0.70	-	125
DMI (kg/day)[L]	4097	7.97	7.86	1.75	21.90	126
FE (kg ADG/kg DMI)[M]	3742	0.09	0.09	0.03	33.24	93
FCR (kg DMI/kg ADG)[N]	3735	12.18	11.16	4.43	36.40	93
RG (kg of ADG/day)[O]	3556	0.00	0.02	0.20	-	93
RIG[P]	3533	0.02	-0.01	0.74	-	93

[A]BW: birth weight;

[B]W120: weight at 120 days of age;

[C]W240: weight at 240 days of age;

[D]W365: weight at 365 days of age;

[E]W450: weight at 450 days of age;

[F]SC365: scrotal circumference at 365 days of age;

[G]SC450: scrotal circumference at 450 days of age;

[H]REA: rib eye area;

[I]BF: backfat thickness;

[J]RF: rump fat thickness;

[K]RFI: residual feed intake;

[L]DMI: dry matter intake;

[M]FE: feed efficiency;

17 [N]FCR: feed conversion ratio;

18 [O]RG: residual average daily gain;

19 [P]RIG: residual intake and average daily gain.

Table 2 - Direct genetic additive (σ^2a), maternal (σ^2m), permanent environmental (σ^2pe), residual (σ^2e) and phenotypic variances (σ^2p), and direct (h^2d) and maternal (h^2m) heritability with their respective standard-error (±SE) for growth, reproductive, carcass and feed efficiency related traits in Nelore cattle

Traits	Genetic Parameters						
	σ^2a	σ^2m	σ^2pe	σ^2e	σ^2p	h^2d±SE	h^2m±SE
BW[A]	5.62	0.98	2.23	9.63	18.45	0.30±0.02	0.05±0.01
W120[B]	88.41	39.22	35.73	177.35	340.72	0.26±0.02	0.12±0.02
W240[C]	174.28	79.97	55.53	382.34	692.13	0.25±0.02	0.12±0.02
W365[D]	330.67	-	-	671.67	1002.34	0.33±0.03	-
W450[E]	342.50	-	-	748.99	1091.49	0.31±0.03	-
SC365[F]	1.79	-	-	2.50	4.29	0.42±0.04	-
SC450[G]	3.08	-	-	3.65	6.73	0.46±0.04	-
REA[H]	16.62	-	-	31.72	48.34	0.34±0.03	-
BF[I]	0.44	-	-	1.52	1.96	0.22±0.02	-
RF[J]	0.64	-	-	1.52	2.16	0.30±0.02	-
RFI[K]	0.09	-	-	0.42	0.51	0.17±0.04	-
DMI[L]	0.21	-	-	0.68	0.89	0.23±0.04	-
FE[M]	0.00003	-	-	0.000404	0.000434	0.07±0.03	-
FCR[N]	0.82	-	-	8.15	8.97	0.09±0.03	-
RG[O]	0.03	-	-	0.15	0.18	0.17±0.05	-
RIG[P]	0.11	-	-	0.43	0.54	0.20±0.05	-

[A]BW: birth weight;

[B]W120: weight at 120 days of age;

[C]W240: weight at 240 days of age;

[D]W365: weight at 365 days of age;

[E]W450: weight at 450 days of age;

[F]SC365: scrotal circumference at 365 days of age;

[G]SC450: scrotal circumference at 450 days of age;

[H]REA: rib eye area;

[I]BF: backfat thickness;

[J]RF: rump fat thickness;

[K]RFI: residual feed intake;

[L]DMI: dry matter intake;

[M]FE: feed efficiency;

[N]FCR: feed conversion ratio;

[O]RG: residual average daily gain;

[P]RIG: residual intake and average daily gain.

Table 3 - Genetic (above the diagonal) and phenotypic (below the diagonal) correlation estimates with their respective standard-error (±SE) between feed efficiency related traits in Nelore cattle

Traits	RFI	DMI	FE	FCR	RG	RIG
RFI[A]	-	0.76±0.05	-0.54±0.06	0.45±0.03	-0.23±0.03	-0.61±0.06
DMI[B]	0.39±0.01	-	-0.50±0.05	0.32±0.02	-0.13±0.02	-0.62±0.02
FE[C]	-0.19±0.03	-0.48±0.03	-	-0.46±0.05	0.28±0.07	0.54±0.04
FCR[D]	0.19±0.03	0.25±0.03	-0.57±0.01	-	-0.58±0.01	-0.55±0.08
RG[E]	-0.12±0.03	0.09±0.03	0.76±0.01	-0.49±0.01	-	0.46±0.03
RIG[F]	-0.76±0.01	-0.36±0.01	0.40±0.03	-0.23±0.03	0.35±0.04	-

[A]RFI: residual feed intake;

[B]DMI: dry matter intake;

[C]FE: feed efficiency;

[D]FCR: feed conversion ratio;

[E]RG: residual average daily gain;

[F]RIG: residual intake and average daily gain.

Table 4 - Genetic and phenotypic correlation estimates with their respective standard-error (±SE) between residual feed intake (RFI), dry matter intake (DMI), feed efficiency (FE), feed conversion ratio (FCR), residual average daily gain (RG), residual intake and average daily gain (RIG) and growth traits in Nelore cattle

Traits	RFI	DMI	FE	FCR	RG	RIG
Genetic correlations						
BW[A]	-0.02±0.03*	0.23±0.02	-0.07±0.02	0.08±0.04	0.17±0.05	0.03±0.03*
W120[B]	0.06±0.01	0.32±0.01	-0.09±0.02	0.09±0.03	0.15±0.01	0.08±0.03
W240[C]	0.07±0.01	0.36±0.03	-0.16±0.01	0.23±0.01	-0.12±0.04	-0.16±0.02
W365[D]	0.22±0.01	0.56±0.08	-0.40±0.04	0.24±0.02	-0.12±0.02	-0.15±0.02
W450[E]	0.19±0.03	0.56±0.08	-0.19±0.03	0.18±0.03	-0.15±0.02	-0.15±0.02
Phenotypic correlations						
BW	-0.01±0.04*	0.15±0.03	-0.09±0.01	0.09±0.04	0.12±0.04	-0.03±0.04*
W120	-0.02±0.01*	0.18±0.05	-0.14±0.03	0.10±0.03	0.13±0.01	-0.04±0.03*
W240	-0.02±0.01*	0.28±0.04	-0.10±0.01	0.17±0.03	0.12±0.03	-0.07±0.02
W365	0.04±0.03*	0.18±0.03	-0.16±0.03	0.16±0.03	-0.19±0.003	-0.06±0.04
W450	0.03±0.03*	0.14±0.03	-0.43±0.03	0.23±0.03	-0.17±0.004	0.02±0.04*

[A]BW: birth weight;

[B]W120: weight at 120 days of age;

[C]W240: weight at 240 days of age;

[D]W365: weight at 365 days of age;

[E]W450: weight at 450 days of age;

*non-significant correlation estimates.

Table 5 - Genetic and phenotypic correlation estimates with their respective standard-error (±SE) between residual feed intake (RFI), dry matter intake (DMI), feed efficiency (FE), feed conversion ratio (FCR), residual average daily gain (RG), residual intake and average daily gain (RIG) and reproductive traits in Nelore cattle

Traits	RFI	DMI	FE	FCR	RG	RIG
Genetic correlations						
SC365[A]	0.17±0.01	0.25±0.01	-0.17±0.07	0.16±0.03	0.06±0.02	0.21±0.02
SC450[B]	0.19±0.01	0.27±0.09	-0.11±0.04	0.10±0.02	0.08±0.02	0.24±0.02
Phenotypic correlations						
SC365	0.01±0.04*	0.18±0.04	-0.07±0.05	0.11±0.04	-0.17±0.05	-0.06±0.05
SC450	0.04±0.05*	0.18±0.05	-0.23±0.04	0.24±0.05	-0.05±0.05*	-0.02±0.01*

[A]SC365: scrotal circumference at 365 days of age;

[B]SC450: scrotal circumference at 450 days of age;

*non-significant correlation estimates.

Table 6 - Genetic and phenotypic correlation estimates with their respective standard-error (±SE) between residual feed intake (RFI), dry matter intake (DMI), feed efficiency (FE), feed conversion ratio (FCR), residual average daily gain (RG), residual intake and average daily gain (RIG) and carcass traits in Nelore cattle

Traits	RFI	DMI	FE	FCR	RG	RIG
Genetic correlations						
REA[A]	0.04±0.01*	0.15±0.01	-0.17±0.03	0.27±0.03	-0.12±0.02	-0.02±0.01*
BF[B]	0.13±0.01	-0.05±0.02	-0.04±0.01*	0.02±0.02*	0.05±0.02	0.07±0.01
RF[C]	0.13±0.01	0.07±0.01	-0.12±0.04	0.18±0.03	-0.09±0.02	0.06±0.01
Phenotypic correlations						
REA	-0.03±0.03*	0.20±0.03	-0.07±0.03	0.04±0.04*	-0.01±0.04*	-0.05±0.04
BF	-0.02±0.03*	0.06±0.02	-0.04±0.03*	0.06±0.03	0.03±0.03*	-0.02±0.03*
RF	0.02±0.03*	0.05±0.03	-0.03±0.03*	0.06±0.01	0.03±0.01*	-0.03±0.03*

[A]REA: rib eye area;

[B]BF: backfat thickness;

[C]RF: rump fat thickness.

Table 7 - Direct genetic gain per generation (diagonal) and relative efficiency of selection (%) for feed efficiency related traits in Nelore cattle[A]

Trait	Relative efficiency of selection (%)					
	RFI	DMI	FE	FCR	RG	RIG
RFI (kg/day)[B]	0.037	97.78	-92.51	96.69	-448.23	-83.31
DMI (kg/day)[C]	96.62	0.101	-93.75	91.53	-681.78	-95.06
FE (kg ADG/kg DMI)[D]	-297.52	-373.74	0.001	-254.12	573.78	322.70
FCR (kg DMI/kg ADG)[E]	314.86	515.02	-197.65	0.246	-244.29	-279.42
RG (kg of ADG/day)[F]	-448.23	-922.41	236.26	-89.33	0.012	93.09
RIG[G]	-95.81	-88.31	92.95	-95.74	96.62	0.049

[A]The traits used a direct selection criterion are those shown in the first column and response traits are those show in the second line of the table. For the direction and response to selection, negative values indicate that the direct selection for increase in *X* traits leads to a reduction in *Y* trait. Conversely, positive values of the relative efficiency of selection indicate that the selection to increase *X* trait also increases *Y* trait.

[B]RFI: residual feed intake;

[C]DMI: dry matter intake;

[D]FE: feed efficiency;

[E]FCR: feed conversion ratio;

[F]RG: residual average daily gain;

[G]RIG: residual intake and average daily gain.

Table 8 - Relative efficiency of selection (%) for residual feed intake (RFI), dry matter intake (DMI), feed efficiency (FE), feed conversion ratio (FCR), residual average daily gain (RG), and residual intake and average daily gain (RIG) when direct selection is performed for growth, reproductive and carcass traits in Nelore cattle[A]

Trait	Relative efficiency of selection (%)					
	RFI	DMI	FE	FCR	RG	RIG
BW[B]	-2138.56	216.30	-392.08	389.01	251.60	1546.40
W120[C]	765.73	167.00	-327.57	371.43	306.29	622.91
W240[D]	669.34	151.38	-187.91	148.22	-390.45	-317.62
W365[E]	185.37	84.70	-65.42	93.63	-339.84	-294.89
W450[F]	221.45	87.39	-142.10	170.08	-280.50	-304.25
SC365[G]	267.31	211.43	-171.53	206.66	757.39	234.72
SC455[H]	228.54	187.07	-253.31	315.95	542.78	196.24
REA[I]	1004.41	311.54	-368.30	98.27	-334.80	-2178.88
BF[J]	384.20	-1161.90	-801.24	1817.05	998.92	773.91
RF[K]	329.01	710.71	-228.71	172.89	-475.24	773.20

[A]The traits used a direct selection criterion are those shown in the first column and response traits are those show in the second line of the table. For the direction and response to selection, negative values indicate that the direct selection for increase in *X* traits leads to a reduction in *Y* trait. Conversely, positive values of the relative efficiency of selection indicate that the selection to increase *X* trait also increases *Y* trait.

[B]BW: birth weight;

[C]W120: weight at 120 days of age;

[D]W240: weight at 240 days of age;

[E]W365: weight at 365 days of age;

[F]W450: weight at 450 days of age;

[G]SC365: scrotal circumference at 365 days of age;

[H]SC450: scrotal circumference at 450 days of age;

[I]REA: rib eye area;

[J]BF: backfat thickness;

[K]RF: rump fat thickness.

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CAPÍTULO 3 - Genomic prediction ability for feed efficiency traits using different models and pseudo-phenotypes under several validation strategies in Nelore cattle

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Abstract

There is a growing interesting to improve feed efficiency traits in cattle. The genomic selection was proposed to improve these traits since they are difficult and expensive to measure. Up to date, there are scarce studies about implementation of genomic selection for feed efficiency traits in indicine cattle under different scenarios of pseudo-phenotypes, models and validation strategies in commercial large scale. Thus, the aim was to evaluate the feasibility of genomic selection implementation for feed efficiency traits in Nelore cattle applying different models and pseudo-phenotypes under different validation strategies. Phenotypic and genotypic information from 4 329 and 3 467 animals were used, respectively, which were tested for residual feed intake, dry matter intake, feed efficiency, feed conversion ratio, residual body weight gain, and residual intake and body weight gain. Six prediction methods were used: single-step genomic best linear unbiased prediction, Bayes A, Bayes B, Bayes Cπ, BLASSO, and Bayes R. Phenotypes adjusted for fixed effects (Y*), estimated breeding value (EBV) and deregressed EBV (DEBV) were used as pseudo-phenotypes. The validation approaches used were: 1) random: the data was randomly divided into ten subsets and the validation was done in each subset at a time; 2) age: the partition into training and testing sets was based on year of birth and testing animals were born after 2016; 3) EBV accuracy: the data was split into two groups, being animals with accuracy above 0.45 the training set; and below 0.45 the validation set. In the analyses that used the Y* as pseudo-phenotype, prediction ability (PA) was obtained by dividing the correlation between pseudo-phenotype and genomic estimated breeding value (GEBV) by the square root of the heritability of the trait. When EBV and DEBV were used as the pseudo-phenotype, the simple correlation of this quantity with the GEBV was considered as PA. The prediction methods show similar results for PA and bias. The random cross-validation

presented higher PA (0.17), than EBV accuracy (0.14) and age (0.13). The PA was higher for Y* than for EBV and DEBV (30.0 and 34.3%, respectively). Random validation presented the highest PA, being indicated for use in populations composed mainly of young animals and traits with few generations of data recording. For high heritability traits, the validation can be done by age, enabling the prediction of the next-generation genetic merit. These results would support breeders to identify genomic approaches that are more viable for genomic prediction for feed efficiency related traits.

Keywords: genomic breeding value, residual body weight gain, residual feed intake, single nucleotide polymorphisms, Zebu

Implications

Genetic selection for feed efficiency allows reduce production costs and the negative effects on the environment. The prediction ability (PA) depends of pseudo-phenotypes and validation approaches used, mainly, for traits that are poor evaluated, as feed efficiency. The genetic parameters and genomic models evaluated provide support for the adoption of these traits on a large evaluation scale. The random cross-validation and phenotype adjusted for fixed effects displayed superior PA. Despite the prediction models show similar PA, the single-step genomic best linear unbiased prediction simplify genomic evaluations, since this model use phenotypes instead of pseudo-phenotypes and accounting with whole population to estimate genomic breeding value.

Introduction

Animal feedstuff plays a significant role in production costs of beef cattle systems (Savieto *et al*., 2014). Thus, there is a big pressure to improve feed efficiency related traits, due to the influence on production costs and to reduce the environmental impacts of livestock. Besides that, competition from beef cattle production with other agribusiness activities has forced breeders and industries to seek new strategies to maximize the efficiency and profitability of meat systems (Olivieri *et al.,* 2016).

In recent years, many efforts were done to improve the ratio of average daily gain (ADG) and dry matter intake (DMI). Novel traits like residual feed intake (RFI), residual body weight gain (RG) (Koch *et al.,* 1963) and residual intake and body weight gain (RIG) (Berry and Crowley, 2012) can be used to identify animals with lower feed intake or higher weight gain (Berry and Crowley, 2012). These traits show the advantage of being phenotypically not associated to growth and body size (Koch *et al.,* 1963; Berry and Crowley, 2012).

The genomic selection was proposed to improve the feed efficiency related traits, since these traits are difficult and expensive to measure, limiting their full-scale use in beef cattle breeding programs (Pryce *et al*., 2012; Silva *et al*., 2016). Several methods are available for genomic prediction, which differ statistically and also for use under commercial conditions (Aguilar *et al*., 2010; Chiaia *et al*., 2018; Daetwyler *et al*., 2013; De los Campos *et al*., 2013; Erbe *et al*., 2012; Habier *et al*., 2011). For Nelore cattle, only traits as ADG, DMI, feed conversion ratio (FCR), and RFI, and models as genomic BLUP, single-step genomic best linear unbiased prediction (ssGBLUP) and Bayes Cπ were evaluated in an experimental herd (Silva *et al.,* 2016).

From the best of our knowledge, there are no reports of pseudo-phenotypes evaluation in the genomic prediction of feed efficiency traits in Nelore cattle (Bolormaa *et al*., 2013; Pryce *et al*., 2012; Silva *et al*., 2016). As pseudo-phenotype or response variable, the true breeding value would be the ideal parameter. However, this value is unknown (De Los Campos *et al*., 2013) and other values were evaluated for this purpose (Chiaia *et al.,* 2018; Fernandes Junior *et al*., 2016), to identify within each scenario, which is ideal to be used. Proper estimation of marker effects requires an adequate pseudo-phenotype to summarize the genetic information on training animals, as well as statistical methods that efficiently associate pseudo-phenotypes to marker information (Ostersen *et al*., 2011). The pseudo-phenotype prediction ability (PA) depends on the structure of the data and pedigree, the EBV accuracy, the availability of phenotypes, genotypes and pedigree, that is, the quantity and quality of the information available (Boddhireddy *et al.,* 2014; Daetwyler *et al.,* 2013; Garrick *et al*., 2009; Neves *et al*., 2014).

Under commercial situations, it is important to enable the prediction of the next-generation genetic merit, using genomic information. Thus, older animals or with more reliable EBV can be used as a reference population to define the prediction equations that will be validated in younger animals or with less accurate EBV, that is indicated when a structured data set with older animals, phenotypic, pedigree and genomic information is available (Habier *et al.,* 2011; Silva *et al*., 2016; VanRaden *et al*., 2009). However, in beef cattle, records from feed efficiency related traits are normally available in young unproven animals, since these traits only have recently been included as a selection criterion, and proven sires only have genomic information.

Thus, the data set for feed efficiency traits have commonly few generations, few animals with progeny record and older animals have low accuracy genetic evaluations. Under these conditions, cross-validation may be feasible (Pérez-Cabal *et al*., 2012; Pryce *et al*., 2012; Silva *et al*., 2016), but, this approach brings as a disadvantage the random formation of training and validation populations, which may result in the use of less accuracy animals for training the prediction equation and in the bias of the estimates (Runcie and Cheng, 2019).

It is important to identify the most appropriate validation approach and pseudo-phenotype for application in different data set structure and population evaluated for feed efficiency related traits, allowing to increase the PA of genomic estimated breeding values (GEBVs).

Most of the previous genomic studies for feed efficiency performed with Zebu breeds were carried out with experimental or small populations with little environmental variation and promising traits as RG and RIG were not evaluated for this breed (Silva *et al.,* 2016). Thus, there is a need to carry out studies with larger sample size to evaluate the implementation feasibility of genomic selection for feed efficiency related traits under different commercial scenarios and data, since feed efficiency related traits are a group of denominated novel traits with scarce phenotyping in bull test stations and complex data structure due to unbalance phenotyping and genotyping.

The aim was to evaluate the feasibility of genomic selection implementation for feed efficiency related traits in Nelore cattle applying different models and pseudo-phenotypes under several validation strategies using records from commercial herds. Preliminary results of this study were published as an abstract (Magnabosco *et al*., 2020), and the same data set was shared with Brunes *et al.* (2020).

Material and methods

Data from the feed efficiency tests carried out between 2011 and 2018, phenotypic and genotypic information of 4 329 and 3 594 animals, respectively, were considered and more details about the data set used was presented by Brunes *et al.* (2020). Animals belonged to 39 farms located in the Midwest, Southeast, Northeast and North Brazilian regions. The Nelore Brazil Breeding Program, coordinated by the National Association of Breeders and Researchers, performs the genetic evaluation of these herds. The relationship matrix was calculated based on pedigree information from 58 374 animals, provided by the National Association of Breeders and Researchers. The data and pedigree have a consistent connection through common sires in the feed efficiency tests and due to achievement of progeny testing for more than 30 years among herds participating in the breeding program (Lobo *et al.,* 2019). A total of 125 feed efficiency tests were performed and animals were evaluated with an average age of 13.5±3.92 months at the beginning of the tests under similar management and environmental conditions in feedlot. Tests were conducted using the same protocol (Mendes *et al.,* 2020). The feed efficiency tests were performed in five different places, three ranches (HoRa Hofig Ramos, Rancho da Matinha and AgroNova) and two research centers (Embrapa Cerrados in Goias and Federal University of Uberlandia). Diets offered over the years differed in composition and ingredients but were formulated based on silage and commercial concentrate, with an average of 64% total digestible nutrients, 13% crude protein, 76% dry matter and formulated for gains of 1.2 kg/day (Mendes *et al.,* 2020). During the tests, the animals' weight was obtained by periodic weighing, and at the beginning and end of

the evaluation period. Roughage, concentrate and wastes samples were collected every week to evaluate chemical composition.

The DNA samples was obtained from hair follicles taken from animals' tails and placed in card with adhesive film. The Nelore cattle were genotyped for single nucleotide polymorphism (SNPs) markers using low-density panel (CLARIFIDE® Nelore 3.1), containing 29 004 molecular markers. DNA extraction and sample genotyping were performed by Zoetis® (Kalamazoo, MI), through its protocol.

Performance traits

The DMI was measured by collective stalls equipped with automated systems (GrowSafeSystem® and Intergado®), for a minimum of 70 days preceded by adaptation. The DMI, measured in kg/day, was obtained by calculating the average of all valid daily intake values during the test period. This parameter was calculated as the amount of individually consumed feed automatically recorded by the electronic systems. The feed efficiency (FE), measured in kg ADG/kg DMI, was obtained as the ratio between ADG and DMI. The FCR, measured in kg DMI/kg ADG, was obtained by the inverse ratio (DMI/ADG). The ADG (kg/day) was estimated by the linear regression coefficient of the weights as a function of the days in test, using the *lm* function of R program (2018) and the following equation:

$$y_{ij} = \alpha_i + \beta_i * DIT_j + \varepsilon_{ij}$$

where: y_{ij} is the jth observation of weight of ith animal; α_i is the intercept of the regression equation which represents the initial weight; β_i is the linear regression coefficient which represents the ADG; DIT_j is the day in the performance test of jth

observation, and; ε_{ij} is the j[th] residual associated to the i[th] record. It was assumed that the residuals were independent and not correlated.

The metabolic body weight was estimated from body weight and ADG, by:

$$MW_i^{0.75} = \left[\alpha_i + \beta_i * (DIT_j/2)\right]^{0.75}$$

where: $MW_i^{0.75}$ is the metabolic body weight of i[th] animal; α_i is the intercept of the regression equation which represents the initial weight; β_i is the linear regression coefficient which represents the ADG, as described and obtained above in estimating ADG.

RFI (kg of DM/day) was estimated, within each contemporary group, by the residual of the DMI regression as a function of ADG and metabolic body weight, using the R program (2018) and the equation below (Koch *et al.,* 1963):

$$y_i = \beta_o + \beta_1 ADG + \beta_2 MW_i^{0.75} + \varepsilon_i \ (RFI)$$

where: *y* is individual dry matter intake of i[th] animal; β_o is the intercept; β_1, and β_2 are the linear regression coefficient of ADG and $MW_i^{0.75}$, respectively; and ε_i is the residual associated to the i[th] observation, i.e. RFI. Regression analysis was performed and no effect of backfat thickness on RFI was observed, thus the RFI was not adjusted for fat thickness.

The RG (Koch *et al.,* 1963; Berry and Crowley, 2012) (kg of ADG/day) was obtained as the difference between the observed ADG and the estimated based on DMI and metabolic body weight. The estimated average daily gain (ADG_{e_i}) was obtained using the *lm* function on the R program (2018), within contemporary group and by:

$$ADG_{e_i} = \beta_o + \beta_1 DMI + \beta_2 MW_i^{0.75} + \varepsilon_i \ (RG)$$

where: β_0 is the intercept, β_1, and β_2 are the regression coefficients of DMI and $MW_i^{0.75}$, respectively; and ε_i is the residual associated to the i[th] observation, i.e. RG.

RIG was calculated as RG-RFI, after standardizing both traits to a variance of 1, allowing of their combination into a single value (Berry and Crowley, 2012). Both traits, RFI and RG, are linear functions of their component traits: DMI, ADG, and metabolic body weight.

Statistical and quality control analyses

The contemporary group was composed by farm, management group, feed efficiency test, sex, year and birth season (dry season from April to September and the rainy season from October to March). The fixed effects included in the contemporary group were those whose p-value was lower than 0.001 obtained from ANOVA results. Records within ±3.5 standard deviations from the contemporary group mean were considered in the analysis. Additionally, all contemporary groups should has at least four animals in order to proceed with the analysis. Descriptive statistics obtained for the traits evaluated are summarized in Table 1.

In the quality control for genomic data, SNPs with minor allele frequency, call rate and p-value for Hardy-Weinberg equilibrium test less than 0.02; 0.95 and 0.15, respectively, were excluded. Only SNPs in autosome chromosomes and with known position according to UMD 3.1 bovine genome were considered. Samples with call rates below to 0.95 were not considered in the analyses. The quality control criteria were defined based on the data set, averages obtained after analysis and in previous studies (Olivieri *et al*., 2016; Silva *et al*., 2016). This process was performed with R program (2018) resulting in a data set with 19 602 SNP and 3 467 animals.

To evaluate the existence of population substructure a principal component analyses was performed using information from SNPs and genomic relationship matrix of individuals who were approved in the quality control criteria (VanRaden, 2008)

(Figure 1) and more details about the data set was described by Brunes *et al.* (2020). The proportion of variance explained by the two first principal components was 33.95%. The PC1 e PC2 did not group the animals into clear-cut clusters, implying that genetic admixture probably existed for the evaluated population. The animals' dispersion in the principal component analysis plot indicated the absence of subgroups among the evaluated animals, since there is no formation of major component. Principal component analyses were also performed between the subsets according to the validation method (Figure 2). The graphic analyses of the validation and training groups, regardless of the method, demonstrates the absence of population substructure formation and reinforces the interrelationship between them. The genetic distance between individuals was calculated based on their genotypes using the method Jukes-Cantor (Jukes and Cantor, 1969) and R program (2018). Genetic distances values were, on average, 0.08 (0.0 to 0.1816), indicating that the data are not dispersed or sub-grouped in whole population (Table 2), as reported by Brunes *et al.* (2020). The genetic distances between training and validation populations displayed the same pattern, with low values and no dispersion, pointed out that considering the animals' genetic structure constitute a unique population.

Estimation of variance components

Variance components and genetic parameters were estimated considering a genomic pedigree-based animal model trough the ssGBLUP (Aguilar *et al.,* 2010). Single-trait analyses were performed using the restricted maximum likelihood method with REMLF90 and AIREMLF90 (Misztal *et al.,* 2017). Initially, the REMLF90 (EM-algorithm) was used and then, the obtained estimates were used as initial values for AIREMLF90 (AI-algorithm), a program used to obtain the standard-error of the

variance components and heritability (Meyer and Houle, 2013). Direct additive genetic and residual effects were included as random effects; the contemporary group and animals' age as covariate were included as a fixed effect. The model used for all traits can be represented as:

$$\boldsymbol{y} = \boldsymbol{X\beta} + \boldsymbol{Z_a} + \boldsymbol{e}$$

where: y is the vector of the observed trait (RFI, DMI, FE, FCR, RG and RIG); X is the incidence matrix of fixed effects; β is the vector of fixed effects; Z are the incidence matrix of direct genetic effects; a is the vector of additive genetic random effects; and e is the vector of residual random effects. It was assumed that $\mathrm{E}[\mathbf{y}] = \mathbf{X\beta}$; with the direct additive genetic, and residual effects assumed normally distributed with mean zero and $\mathrm{Var}(\boldsymbol{a}) = \mathbf{H} \otimes \mathbf{S}_{\mathrm{a}}$, and $\mathrm{Var}(\mathbf{e}) = \mathbf{I} \otimes \mathbf{S}_{\mathrm{e}}$; in which $\mathbf{S}_{\mathrm{a}}$ and $\mathbf{S}_{e}$ is the additive genetic and residual covariance matrix, respectively, and $\mathbf{I}$ is an identity matrix of appropriate order.

The ssGBLUP is a modification of the traditional BLUP, where the inverse of the numerator relationship matrix (A^{-1}) was replaced by H^{-1} (Aguilar *et al.,* 2010), which combines pedigree and genomic information. The inverse of H matrix was obtained as (Aguilar *et al.,* 2010):

$$H^{-1} = A^{-1} + \begin{bmatrix} 0 & 0 \\ 0 & G^{-1} - A_{22}^{-1} \end{bmatrix}$$

where: H is the relationship coefficients matrix between the animal; A_{22} is an additive relationship matrix for the genotyped animals; and G is the genomic relationship matrix. The G matrix was created as proposed by VanRaden (2008) as follow:

$$G = \frac{ZDZ'}{\sum_{i=1}^{M} 2p_i(1-p_i)}$$

Where, Z is an incidence matrix adjusted for allele frequencies; D is a diagonal matrix of weights for SNP variances; M is the number of markers, and p_i represented the minor allele frequency of the i[th] SNP. These factors were obtained ensuring that the average diagonal in G is close to that of A_{22}.

Genomic analyses

Three pseudo-phenotypes were used in the genomic analyses: EBV, deregressed estimated breeding value (DEBV) and phenotype adjusted for fixed effects (Y*). The EBVs obtained in the genomic pedigree-based animal model analyses were deregressed using the method proposed by Garrick *et al.* (2009), with the support of the DPR package (Lopes, 2017) of R program (2018). The Y* was obtained based on the phenotype observed that was adjusted using an animal model considering the fixed effects of the contemporary group and age of evaluation of feed efficiency:

$$y_{ij}^{*} = \mu + CG_j + \beta age + e_{ij}$$

where: y_{ij}^{*} is the j[th] observation of phenotype adjusted for fixed effects of i[th] animal; μ is the average of the data; CG_j is the fixed effect of the j[th] contemporary group; β is the regression coefficients of age; e_{ij} is the random effect of the j[th] residue of the i[th] observation; with $\mu = 0$ and variance=σ^2_e.

The EBVs and DEBVs accuracy were calculated using the formula below:

$$Acc = 1 - \sqrt{\left(\frac{PEV}{\sigma_a^2}\right)}$$

where: PEV is the variance of prediction error; and; σ_a^2 is the additive genetic variance of the trait. Table 3 shows the descriptive statistics and accuracy for pseudo-phenotype used in genomic analyses.

The general model used for genomic predictions was:

$$\boldsymbol{y} = \boldsymbol{\mu} + \sum_{\boldsymbol{j=1}}^{\boldsymbol{k}} \boldsymbol{Z_{ij} a_j} + \boldsymbol{e}$$

where: y is the pseudo-phenotype vector (Y*, EBV ou DEBV) of i[th] animal; μ is an overall constant; k is the number of SNP; Z_{ij} is a genotype indicator variable for individual i at locus j; a_j for j = *1, 2…*; and e is residual effect vector is the residual associated to the observation on individual i. SNPs were coded as 0, 1 and 2 for AA, AB e BB, respectively. The residual distribution vector (e) was:

$$e \sim N(0, I\sigma_e^2)$$

where: σ_e^2 is residual variance.

For Bayesian analyses, Gibbs chains of 200 000 iterations was generated, with a burn-in period of 150 000 cycles and a sampling interval of 10. The burn-in period, thin and chain convergence were verified by visual inspection of a posteriori means of additive and residual genetic variances, using BOA package of R program (2018), with trace plots for visual inspection, autocorrelation and Geweke method (Geweke, 1992).

Single step genomic best linear unbiased prediction

The animal model was applied to the ssGBLUP method (Aguilar *et al.,* 2010). The model used was the same one used to estimate variance components, as described above, by combining A and G from the H matrix.

Bayes A

For Bayes A (Meuwissen *et al.,* 2001), it was assumed that the prior conditional distribution of a marker effect (a_j) is Gaussian, with mean equal to zero and independent variance σ^2_{aj}. The variance associated with the effect of each marker has an inverse χ^2 prior distribution:

$$p(\sigma^2_{aj}) = \chi^{-2}(\sigma^2_{aj}|v, S^2)$$

where: v is degrees of freedom, and; S^2 is scale parameters. After these specifications, the marginal prior distribution of each marker effect is:

$$p(a_j \mid v, S^2) = \int N(a_j \mid 0, \sigma^2_{a_j}) \chi^{-2}(\sigma^2_{a_j} \mid v, S^2) \partial\sigma^2_{a_j}$$

which presents distribution *t-Student t*$(0, v_a, S^2_a)$ (Rosa *et al.,* 2003):

$$p(a_j \mid v, S^2) = t(0, v, S^2)$$

Bayes B

In Bayes B (Meuwissen *et al.,* 2001), it was assumed that most markers a have null effect and only a few contribute to the genetic variance (σ^2_{aj}), conditional on the specific variance of each marker, non-zero and Gaussian distribution $N(a_j|0, \sigma^2_{aj})$. Therefore, the distribution of marker effects can be described with the mixed model:

$$p(a_j \mid \sigma^2_{a_j}, \pi) = \begin{cases} 0 & \text{with probability } \pi \\ N(0, \sigma^2_{aj}) & \text{with probability } (1-\pi) \end{cases}$$

where: π is the proportion of makers with null genetic effects. Similar to Bayes A, this model shows inverse χ^2 prior distribution, thus, marginally, after integrating the variances of the markers:

$$p(a_j \mid \pi) = \begin{cases} 0 & \text{with probability } \pi \\ t(0, v, S^2) & \text{with probability } (1-\pi) \end{cases}$$

Thereby, Bayes B can be reduced to Bayes A assuming that $\pi = 0$. S^2, given by:

$$S^2 = \frac{\sigma_a^2(\nu - 2)}{\nu}$$

where:

$$\sigma_a^2 = \frac{\sigma_S^2}{(1-\pi)\sum_{j=1}^{K} 2p_j(1-p_j)}$$

σ_a^2 is the additive genetic variance; p_j is the frequency of *j*th SNP; σ^2_S is the additive genetic variance explained by SNPs, and; π is the probability that *j*th SNP has null effect (Habier *et al.,* 2011).

Bayes Cπ

In Bayes Cπ method, proposed by Habier *et al.* (2011), the markers effects have a common variance, following a scaled inverse χ^2 prior, with V_a degrees of freedom and S_a^2 a scale parameter. As a result, the effect of an SNP fitted with probability (1 – π) and presents a mixture of multivariate student's t-distribution $t(0, V_a, IS_a^2)$, where π is the probability of a marker presenting null effect and has a uniform prior distribution (0, 1).

In this method, π is estimated from the analyzed data. Subsequently, the inclusion or exclusion of each marker in the model was performed by an indicator variable δ_j, which is equal to 1 if the marker *j* is fitted in the model, otherwise, it is zero. The common effect variance is sampled from full-conditional posterior, which presents scaled inverse χ^2 distribution with degrees of freedom $\widetilde{V_a} = V_a + m^t$ and scale:

$$\widetilde{S_a^2} = (v_a S_a^2 + \sum_{j=1}^{k} a_j^2)/\widetilde{v_a}$$

where: m^t is the number of markers fitted with non-zero effects in iteration *t*.

Bayesian Least Absolute Shrinkage and Selection Operator

In the bayesian least absolute shrinkage and selection operator (BLASSO) (Park and Casella, 2008), the conditional prior distribution of each marker effect

$$p\left(a_j \mid \tau_j^2, \sigma_e^2\right),$$

is Gaussian with a zero-mean and marker-specific prior variance, independent from each other. Thus,

$$p\left(a_j \mid \tau_j^2, \sigma_e^2\right) = \prod_{j=1}^{p} N\left(a_j \mid 0, \tau_j^2 \sigma_e^2\right)$$

This prior induces marker-specific shrinkage, whose extent depends on τ_j^{-2}. The variances parameters (τ_j^{-2}) are assigned exponential IIID prior:

$$p\left(\tau_1^2, \tau_2^2, ..., \tau_K^2 \mid \lambda\right) = \prod_{j=1}^{K} Exp\left(\tau_j^2 \mid \lambda\right),$$

and a Gamma process is assumed as the prior distribution of the square of regularization parameter λ (Park and Casella, 2008),

$$p\left(\lambda^2\right) = Gamma\left(r, \theta\right)$$

Under these settings, the marginal prior of each marker is a double exponential, as follows:

$$p\left(a_j \mid \lambda\right) = \int N\left(a_j \mid 0, \sigma_e^2 \tau_j^2\right) Exp\left(\tau_j^2 \mid \lambda^2\right) \partial \tau_j^2$$

Finally, the residual variance (σ_e^2) is assigned and a priori density of X^2 scaled inverse prior density, with degrees of freedom df_e, and scale parameter S_e.

Bayes R

In Bayes R (Erbe *et al.,* 2012), which is an extension of Bayes Cπ with the assumption that the SNP effects (g) are derived from a mixture of normal distributions N(0, σ^2_k), according to the ratio vector

$$\boldsymbol{PR} = \{Prk|k = 1,2,3,4\}$$

Variances of each component were fixed

$$\sigma^2_K = \{0, 0.0001 * \sigma^2_g, 0.001 * \sigma^2_g, 0.01 * \sigma^2_g\},$$

where σ^2_g is the total genetic variance. The prior distribution of the probability vector $\mathrm{pr} = (pr1, pr2, pr3, pr4)$ is a Dirichlet distribution (a multivariate generalization of a beta distribution), with α=1 (where α is a vector 4 x 1 of pseudo-counts, all with value 1, providing prior not informative). The Dirichlet distribution is a conjugate of the prior multinomial distribution, so that the posterior distribution of **pr** é ~Dir (α + β), where β is a vector containing the number of SNPs in each distribution, estimated from the data.

Fixed effects included in the model were the same as ssGBLUP describe above, however, a residual polygenic effect was added in Bayes R, with a covariance structure proportional to the relationship matrix.

Estimation of genomic breeding values

Based on the solutions of SNP effects estimated by the models studied, the direct genetic value were calculated using the following formula:

$$DGV_i = \sum_{j=1}^{p} w_{ij}\hat{g}_j$$

where: DGV_i is the direct genetic value; p is the number of SNPs; w_{ij} is the genotype of animal *i* for SNP *j* (coded as 0, 1 or 2); and $\widehat{g_j}$ is the estimated SNP substitution effect for SNP *j* that was estimated from the training population. The genomic breeding values prediction was performed using the program BLUPF90 (Misztal *et al.,* 2017) to ssGBLUP; BGLR (Bayesian Generalized Linear Regression) (Campos and Rodriguez, 2015) from R Program (2018) to Bayes A, Bayes B, Bayes Cπ and BLASSO; and Bayes R with scripts supported by R Program (2018), to the method of the same name.

Validation and model comparison

Three validation strategies were used: age, EBV accuracy and random cross-validation. For age, the animals were divided into two groups, being the animals born between 2010 and 2016, the training set; and animals born in 2017 the validation set. For EBV accuracy, the animals were divided into two groups, being animals with accuracy above 0.45 the training set; and below 0.45 the validation set. Considering the random cross-validation strategy, the analyses were conducted repeatedly, considering the k-fold technique. The whole data set is randomly partitioned into ten subsets (folds) each of approximately equal sizes. Then, nine subsets were used for training the genomic prediction model and the remaining subset was used for validation (Resende *et al.,* 2012). At each repetition, cross-validation was performed in the group not used in the training set. After ten repetitions, animals from the ten sets were part of the validation group and had their genomic values predicted. All validation analyses, was implemented on R program (2018).

The GEBVs were calculated by an index combining parent average and direct genetic value (VanRaden *et al.,* 2009):

$$GEBV_i = b_{DGV}DGV + b_{PA}PA$$

where: PAV is the parent average.

In the analyses that the used phenotype or Y* as pseudo-phenotype, PA was obtained by dividing the correlation between pseudo-phenotype and GEBV by the square root of the heritability of the trait (Pryce *et al.,* 2012). This quantity is an approximation of the correlation between GEBV and true breeding value, which corresponds to true accuracy (Meuwissen *et al.*, 2013). When EBV and DEBV were used as the pseudo-phenotype, the simple correlation of this quantity with the GEBV was considered as PA as an empirical measure of accuracy. In scenarios that used EBV or DEBV, the correlation between them and GEBV may be seen as an upper limit of the correlation between true breeding value and GEBV, which corresponds to a nonbiased accuracy estimate (Boddhireddy *et al.,* 2014).

The regression between the pseudo-phenotype and the GEBVs was used to express the GEBV bias towards them, i.e. the magnitude of inflation/deflation in relation to the GEBV. Hypothesis tests were performed to check the adequacy of the regression equations, through analysis of variance (ANOVA) (Montgomery and Runger, 2013). These hypothesis tests were performed considering a significance level of 0.05. The mean square error, which measures the individual differences between the values predicted by the model, was also calculated.

Results

Variance components and heritability obtained for evaluated traits are summarized in Table 1.

Table 4 shown the PA values obtained for feed efficiency related traits considering validation approaches and pseudo-phenotypes. For traits with low heritability estimates, like FE and FCR, the average PA were lower, 0.07±0.03 and 0.09±0.03, respectively. Therefore, compared to FCR and FE, higher selection response may be expected when using DMI, RFI, RG and RIG as selection criterion. As expected, traits showing higher heritability estimates also displayed higher PA, such as DMI which show heritability estimates of 0.23±0.04 and PA of 0.20±0.05. The prediction models display similar PA, whose average values were 0.14±0.06, 0.14±0.06, 0.14±0.06, 0.13±0.06, 0.13±0.06, and 0.15±0.06 for Bayes A, Bayes B, Bayes Cπ, BLASSO, Bayes R and ssGBLUP, respectively (Table 4).

For cross-validation approaches the highest PA were achieved by random, and the lowest PA was obtained by using the age. The exception to this pattern was observed for DMI, which presented the highest heritability, and similar results for all validation approaches.

The phenotype adjusted for fixed effects as pseudo-phenotype displayed higher PA compared to EBV and DEBV. The average PA using EBV and DEBV as pseudo-phenotype were lower than those obtained with Y*, 30.0 and 34.3%, respectively. The EBV and DEBV as pseudo-phenotype displayed similar results for PA, 0.12±0.05 and 0.11±0.04, respectively.

In general, the regression coefficients were similar for all the models, validation approaches and pseudo-phenotype; and it were close to 1 (1.06±0.06) (Table 5), pointed out unbiased predictions.

The prediction models, validation approaches and pseudo-phenotype show similar mean squared error (0.05±0.05), except for the adjusted phenotype (0.58±1.93) (Supplementary Table S1).

Discussion

Heritability estimates for RFI, DMI, RG and RIG were moderate and similar to those reported for beef cattle, ranging from 0.13 to 0.28 for RFI; from 0.25 to 0.36 for DMI; from 0.11 to 0.36 for RG and from 0.12 to 0.34 for RIG (Berry and Crowley, 2012; Ceacero *et al*., 2016; de Moraes *et al*., 2017; de Oliveira *et al*., 2014; Grion *et al*., 2014; Olivieri et al., 2016; Silva *et al.*, 2016). For FE and FCR, heritability estimates were lower than those presented in the literature for Nelore cattle, whose estimates range from 0.13 to 0.17 (FE) and 0.11 to 0.19 (FCR) (Ceacero *et al.*, 2016; Grion *et al.*, 2014; Olivieri *et al.*, 2016; Polizel *et al*., 2018; Silva *et al*., 2016). Compared to other feed efficiency related traits, the lower heritability obtained for FCR and FE is due to these traits are obtained as a ratio (Ceacero *et al.* 2016).

Higher PA for higher heritability traits was also observed by Silva *et al.* (2016) whom evaluated a Nelore cattle experimental population and reported that ADG and DMI shown the highest heritability (0.39 to 0.43, respectively) and PA (0.45 to 0.47 and 0.45 and 0.49, respectively). Similarly, Bolormaa *et al.* (2013), evaluating *Bos Taurus* (1 743; 223; 717 and 613 Angus, Murray Grey, Shorthorn and Hereford cattle, respectively)*, Bos indicus* (3 384 Brahman cattle) and composite beef cattle (550, 598 and 1 826 Belmont Red, Santa Gertrudis and Tropical Composites cattle) for RFI, DMI, ADG and metabolic body weight, observed higher PA (0.13 to 0.36) for higher heritability traits (0.36 to 0.56).

Similar results for PA between the genomic methods are in agreement with the literature (De Los Campos *et al.*, 2013; Lourenço *et al*., 2015; Strandén *et al*., 2017). These results can be attributed to the moderate to high accuracy of the EBV and DEBV as pseudo-phenotype (Table 3). The ssGBLUP does not require pre-

processing of phenotypes compared to multi-step methods (Aguilar *et al.*, 2010; Christensen *et al*., 2012), accounting for the entire population structure to estimate GEBVs (Lourenco *et al.,* 2014). However, when high accuracy pseudo-phenotypes are used, the markers effects may be estimated properly in bayesian methods. The similarity between the prediction methods can also be attributed to the large number of records and because most animals with phenotypes had genotypic information, in these conditions frequentist and bayesian methods reach the same PA (Meuwissen, 2009).

Another reason for the similarity between the prediction methods is the complex and polygenic nature of the feed efficiency traits, since different models tend to show similar predictive ability when the traits are affected by many small-effect loci (De Los Campos *et al.*, 2013). In this case, prediction models show similar PA, since the genetic architecture appeared to approach the infinitesimal model (Lee *et al*., 2017). Still, other factors besides the PA must be taken into consideration in choosing the genomic prediction method used, as data set. The ssGBLUP may be indicated for population that have genotyped and non-genotyped animals and the individuals are related and connected through the pedigree (Silva *et al.,* 2016). Since, this method associates phenotypic information from non-genotyped animals that are related to genotyped animals via a combined relationship matrix and using all available information (Lourenco *et al.,* 2014; Silva *et al.,* 2016). In ssGBLUP, the information from animals' relatives are take in account priority rather than the individual information (Silva *et al.,* 2016). Another advantage of ssGBLUP was the lower computational demand and time, also simplifying the evaluations and allowing the selection of animals only with genotype information (Aguilar *et al.*, 2010). The key

aspect of genomic selection implementation is obtaining GEBVs for the selection of non-phenotyped animals.

On the other hand, frequentist methods require more records to reach a high PA than does a Bayesian method, and when the number of records is small and the marker density is high, bayesian methods may show superior PA (Meuwissen, 2009). For data set with missing pedigree, genomic prediction using ssGBLUP can be compromised, increasing bias and leading to convergence problems and incompatibility between kinship and genomic matrices (Misztal *et al*., 2013; Tonussi *et al*., 2017). In addition, for data set with missing pedigree, pseudo-phenotypes can be of low accuracy, compromising genomic selection. For these data sets the bayesian methods and Y* as pseudo-phenotype can be recommended.

The low PA for validation using age or EBV accuracy may be due to few generations and few animals with progeny record evaluated for the feed efficiency traits. Generally, older animals have more information and EBV with higher accuracy to be used as a training population, which does not apply here, as these traits were recently included as a selection criterion, so the training and validation population display the same information available. As a result, there is no gain in PA using older animals or based on accuracy. Moreover, validation with age and EBV accuracy grouping gives no consideration of the relationship between the evaluation subsets. Prediction ability depend not just on a large population, but also on how closely related the individuals are. In addition, animals grouping by age or EBV accuracy can lead to higher variation in the number of animals in training and validation sets when compared to the random method, which may also have influenced PA (VanRaden *et al.,* 2009).

In the randomness approaches, predictions may be optimistically biased because the individuals were more related than validation by age or EBV accuracy. This leads to higher PA, even for low or moderate heritability traits (Pérez-Cabal *et al.* 2012). Results reported by Silva *et al.* (2016), whom evaluated RFI, FCR, ADG, and DMI, are in agreement with this study, where higher PA values with random cross-validation were obtained compared to grouping by animal's age. Evaluating RFI and weaning weight in Holstein heifers Pryce *et al.* (2012) also observed that the GEBVs PA is influenced by the relationship between two individuals, and higher levels of genomic relationships among animals, more accurate are the predicted genomic values. Thus, in a related population, with young animals and without progenies cross-validation can be used to better test results and prediction and lead to drawn robust conclusions. On another hand, for high heritability traits the genomic prediction using validation based on age or EBV accuracy may be performed without losing PA. The feasibility of using older animals to estimate prediction equations for traits with higher heritability and to validate in young animals would enable predict next- generations' performance and anticipate evaluation and decision-making.

The ratios between genetic signal and noise differ for Y*, EBV and DEBV (Daetwyler *et al*., 2013). Thus, different results for genomic predictions using each one of the pseudo-phenotype were expected and an advantage for either one of these depends on the data set used and the specific application (Boddhireddy *et al*., 2014). EBV accuracies are influenced by the trait heritability and this fact supports the superiority of the PA obtained with the adjusted phenotype over EBVs and DEBVs, mainly for FCR and FE. Previous studies also reported higher PA using Y* as pseudo-phenotype to estimate markers effects (Fernandes Júnior *et al.,* 2016). When low heritability or low EBV accuracy trait and population with missing pedigree is

evaluated, the use of Y* as pseudo-phenotype may be indicated. The adoption of Y* can be a strategy for commercial populations that present phenotype and genotype, but without pedigree records.

The similarity in PA using EBV and DEBV as pseudo-phenotype may be attributed to the full knowledge of the kinship matrix (Chiaia *et al.,* 2018), increasing the reliability of the deregressed EBV. So, for data set without missing pedigree, use of DEBV as pseudo-phenotype brings the same PA than EBV, with the advantage to avoid double-counting of information and double shrinkage of the direct genomic values by using EBVs as pseudo-phenotypes (Garrick *et al*., 2009). However, the use of multiple sires and the unknown parental identification are common in extensive beef cattle production systems, which results in missing pedigree, in this case the use of Y* as pseudo-phenotype for bayesian models or phenotype for ssGBLUP can be recommended.

Is important to emphasize that higher PA values for feed efficiency related traits were obtained by Silva *et al.* (2016) evaluating Nelore cattle. This difference may be due to the closely related experimental population composed by a unique herd with smaller environmental variance. This study evaluated animals from different herds and subjected to varying environmental conditions, which may lead to the lowest additive genetic variance. Nevertheless, the use of genomic information to predict breeding values proved to be a feasible alternative, aiming the accurate identification of more efficient animals for feed utilization. Considering the genomic PA for feed efficiency is around 0.30 in beef and dairy cattle (Mujibi *et al.,* 2011; Pryce *et al.,* 2012; Bolormaa *et al.,* 2013), and results obtained in this study are within the range observed in preview reports.

574 The small difference between models for prediction bias can be attributed to the
575 larger sample size (Silva *et al*., 2016), since in this case, pseudo-phenotypes are
576 more accurate (Table 3), reducing the differences between models. In addition, the
577 most animals with phenotype have genotypic information in this study, as mentioned
578 before, reducing the predictive advantage of ssGBLUP. The higher number of
579 phenotyped and genotyped animals may result in a decrease in prediction bias
580 (VanRaden *et al.,* 2009), even for low heritability traits and regardless of the
581 prediction model used. In fact, Bolormaa *et al.* (2013) reported that traits with a large
582 number of evaluated and genotyped animals provided less biased GEBVs prediction.
583 Another factor that influenced the prediction bias is the kinship matrix between the
584 animals of the validation and training population. Although most of the evaluated
585 animals are not a selected population for feed efficiency, and come from several
586 commercial herds with high genetic diversity, the level of genomic relationship
587 between individuals is high, since there are several sires that connect the feed
588 efficiency tests. Genomic predictions tend to be more precise when animals in the
589 validation population are related to animals in the training population (Saatchi *et al.,*
590 2011). This pattern agrees with the results presented by Pryce *et al.* (2012),
591 evaluating feed efficiency Holstein heifers.
592 The similarity between the models based on bias may be attributed also to the
593 polygenic nature of the evaluated traits. The feed efficiency traits show complex
594 nature and controlled by several quantitative trait loci with small effect (Rolf *et al.,*
595 2012; Santana *et al.,* 2014; Olivieri *et al.,* 2016). In accordance, Daetwyler *et al.*
596 (2013) observed that the models show the same prediction capacity when the traits
597 are affected by many small-effect loci.

The highest mean square error observed for Y* may be due to this parameter follows the magnitude of the pseudo-phenotype. Fernandes Junior *et al.* (2016), evaluated carcass traits in Nelore cattle and also reported variation in mean square error as a function of the magnitude of the trait. These results do not necessarily suggest the rejection of models with high mean square error using Y* when compared to other pseudo-phenotypes included in this study, since the adjusted phenotype as a pseudo-phenotype showed higher PA and similar bias.

The use of genomic information to predict breeding values proved to be a feasible alternative, aiming the accurate identification of animals with better feed utilization. Residual body weight gain and residual intake and body weight gain show similar PA to residual feed intake, being an effective selection criterion for feed efficiency. The prediction methods show similar results for PA and bias. Random cross-validation schemes presented the highest PA than EBV accuracy and age, being indicated for use in populations composed mainly of young animals, and for traits with few generations of data recording. For high heritability traits, the validation can be done by age reaching the same prediction ability as random validation, enabling the training in older animals, validation in young animals and the prediction of the next-generation genetic merit, using genomic information. The adjusted phenotype pseudo-phenotype was more appropriate to estimate marker effects when few generations of phenotypes and genotypes of young animals are available and pedigree information is not available. The results from this study would support breeders to identify prediction methods, pseudo-phenotypes and validation approaches that are more viable for genomic prediction for feed efficiency related traits, considering the data structure and information available for traits with different genetic background.

Ethics approval

The research project was approved by the Committee on Ethics in the Use of Animals (CEUA/PRPI) of the Federal University of Goiás (UFG), according to protocol N° 088/18 issued by this institution.

Data and model availability statement

The data that support the findings of this study are available on request from the corresponding author upon reasonable request. The data are not publicly available due to privacy or legal restrictions, because it belongs a commercial breeding program.

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Declaration of interest

The authors declare that they do not have any conflict of interest regarding the topics approached within this study.

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Table 1 Number of observations (N), phenotypic mean, standard-deviation (SD), number of contemporary group (N° CG), additive genetic variance (σ^2a), residual variance (σ^2e) and heritability ± standard-error (h^2 ±SE) for feed efficiency related traits in Nelore cattle*

Trait	N	Mean	Median	SD	N° CG	σ^2a	σ^2e	h^2±SE
RFI	4 080	0.00	0.03	0.70	125	0.09	0.042	0.17±0.04
DMI	4 097	7.97	7.86	1.75	126	0.21	0.68	0.23±0.04
FE	2 242	0.09	0.09	0.03	93	0.000030	0.000404	0.07±0.03
FCR	2 235	12.18	11.16	4.43	125	0.80	8.14	0.09±0.03
RG	2 056	0.00	0.02	0.20	93	0.03	0.16	0.17±0.05
RIG	2 033	0.02	-0.01	0.74	93	0.11	0.43	0.20±0.05

*This table was previously presented in Brunes *et al.* (2020). RFI: residual feed intake; DMI: dry matter intake; FE: feed efficiency; FCR: feed conversion ratio; RG: residual body weight gain; RIG: residual intake and body weight gain.

856 ***Table 2*** Descriptive analysis of genetic distance in Nelore cattle*

Statistics	Mean	Median	Minimum	Maximum	1° quartile	3° quartile
Whole population	0.0865	0.0835	0.0000	0.1816	0.0526	0.1030
Between folds of random validation	0.0912	0.0971	0.0000	0.1710	0.0421	0.0991
Training and validation population for age approach	0.1161	0.1158	0.0002	0.1816	0.0635	0.1174
Training and validation population for estimated breeding value accuracy	0.1095	0.1087	0.0001	0.1796	0.0603	0.1125

857 *This table was previously presented in Brunes *et al.* (2020).

858 ***Table 3*** Number of observations (N), mean, standard deviation (SD), minimum,
859 maximum and average accuracy±standard deviation (Accuracy±SD) of adjusted
860 phenotype (Y*), estimated breeding value (EBV) and deregressed estimated
861 breeding value (DEBV) for feed efficiency related traits in Nelore cattle

Trait	Pseudo-phenotype	N	Mean	SD	Minimum	Maximum	Accuracy+SD
	Y*[1]	4 103	0.0008	0.69	-3.7449	2.7051	-
RFI	EBV	3 467	-0.0533	0.11	-0.5373	0.3323	0.85±0.08
	DEBV[2]	3 467	-0.0807	0.17	-0.9679	0.6123	0.66±0.03
	Y*	4 106	7.9718	0.91	3.5410	11.2700	-
DMI	EBV	3 467	-0.0828	0.15	-0.9183	0.6649	0.48±0.04
	DEBV	3 467	-0.1583	0.29	-1.8029	1.2328	0.52±0.01
	Y*	2 246	0.0916	0.02	0.0223	0.2584	-
FE	EBV	3 467	0.0007	0.00	-0.0030	0.0044	0.42±0.02
	DEBV	3 467	0.0013	0.00	-0.0059	0.0087	0.51±0.01
	Y*	2 239	12.1776	2.92	0.5220	26.7131	-
FCR	EBV	3 467	-0.1216	0.24	-1.1414	0.8668	0.46±0.05
	DEBV	3 467	-0.4047	0.42	-2.0524	1.5146	0.57±0.01
	Y*	2 059	0.0045	0.13	-0.6409	0.5181	-
RG	EBV	3 467	0.0037	0.02	-0.1130	0.0910	0.57±0.04
	DEBV	3 467	-0.0131	0.06	-0.2662	0.3618	0.50±0.03
	Y*	2 062	0.0189	0.71	-2.6711	3.5023	-
RIG	EBV	3 467	0.1051	0.15	-0.5773	0.9320	0.73±0.14
	DEBV	3 467	0.0963	0.16	-0.6977	1.3512	0.72±0.03

862 RFI: residual feed intake; DMI: dry matter intake; FE: feed efficiency; FCR: feed conversion ratio; RG:
863 residual body weight gain; RIG: residual intake and body weight gain; [1]The Y* was obtained based on
864 the phenotype observed that was adjusted using an animal model considering the fixed effects of the
865 contemporary group and age of evaluation of feed efficiency; [2]The DEBV was obtained by the EBV
866 deregression using the method proposed by Garrick *et al*. (2009).

867 **Table 4** *Prediction ability of breeding genomic values for residual feed intake (RFI),*
868 *dry matter intake (DMI), feed efficiency (FE), feed conversion ratio (FCR), residual*
869 *body weight gain (RG) and residual intake and body weight gain (RIG) in Nelore*
870 *cattle using different pseudo-phenotypes, models and validation approaches*

Trait	Pseudo-phenotype	BayesA	BayesB	BayesCπ	Blasso	BayesR	ssGBLUP
Random							
	Y						0.221 ±0.02
	Y*	0.264 ±0.01	0.251 ±0.02	0.272 ±0.01	0.259 ±0.02	0.262 ±0.02	
RFI	EBV	0.143 ±0.01	0.121 ±0.01	0.182 ±0.02	0.153 ±0.01	0.152 ±0.01	
	DEBV	0.112 ±0.01	0.148 ±0.01	0.134 ±0.02	0.136 ±0.01	0.121 ±0.01	
	Y						0.272 ±0.01
	Y*	0.339 ±0.01	0.300 ±0.01	0.337 ±0.01	0.345 ±0.01	0.345 ±0.01	
DMI	EBV	0.221 ±0.02	0.161 ±0.01	0.239 ±0.02	0.23 ±0.02	0.239 ±0.02	
	DEBV	0.121 ±0.01	0.198 ±0.01	0.235 ±0.02	0.211 ±0.01	0.253 ±0.02	
	Y						0.143 ±0.01
	Y*	0.170 ±0.01	0.144 ±0.01	0.126 ±0.01	0.194 ±0.02	0.157 ±0.01	
FE	EBV	0.109 ±0.01	0.107 ±0.01	0.162 ±0.03	0.124 ±0.01	0.103 ±0.01	
	DEBV	0.095 ±0.01	0.106 ±0.01	0.123 ±0.01	0.103 ±0.00	0.088 ±0.01	
	Y						0.120 ±0.01
	Y*	0.130 ±0.01	0.150 ±0.01	0.113 ±0.01	0.147 ±0.01	0.148 ±0.01	
FCR	EBV	0.168 ±0.02	0.091 ±0.01	0.151 ±0.02	0.167 ±0.02	0.134 ±0.01	
	DEBV	0.089 ±0.01	0.089 ±0.01	0.089 ±0.01	0.065 ±0.00	0.118 ±0.01	
	Y						0.130 ±0.02
RG	Y*	0.223 ±0.01	0.221 ±0.01	0.239 ±0.01	0.214 ±0.02	0.200 ±0.02	
	EBV	0.114	0.105	0.139	0.127	0.124	

		±0.01	±0.01	±0.01	±0.01	±0.01	
RG	DEBV	0.109 ±0.01	0.108 ±0.01	0.117 ±0.01	0.107 ±0.01	0.123 ±0.02	
	Y						0.214 ±0.02
RIG	Y*	0.245 ±0.02	0.270 ±0.02	0.244 ±0.01	0.251 ±0.02	0.200 ±0.02	
	EBV	0.121 ±0.01	0.098 ±0.01	0.121 ±0.01	0.111 ±0.01	0.141 ±0.01	
	DEBV	0.154 ±0.01	0.126 ±0.01	0.128 ±0.01	0.138 ±0.01	0.16 ±0.01	
Age							
	Y						0.16
RFI	Y*	0.19	0.18	0.18	0.19	0.22	
	EBV	0.10	0.11	0.10	0.11	0.14	
	DEBV	0.11	0.11	0.11	0.12	0.12	
	Y						0.24
DMI	Y*	0.25	0.24	0.25	0.24	0.22	
	EBV	0.15	0.11	0.21	0.16	0.14	
	DEBV	0.17	0.16	0.16	0.15	0.19	
	Y						0.08
FE	Y*	0.08	0.06	0.10	0.06	0.07	
	EBV	0.04	0.03	0.03	0.04	0.04	
	DEBV	0.06	0.04	0.06	0.04	0.09	
	Y						0.10
FCR	Y*	0.13	0.15	0.12	0.16	0.13	
	EBV	0.06	0.06	0.05	0.06	0.08	
	DEBV	0.05	0.06	0.05	0.06	0.08	
	Y						0.15
RG	Y*	0.19	0.18	0.18	0.16	0.08	
	EBV	0.10	0.10	0.11	0.11	0.06	
	DEBV	0.11	0.12	0.10	0.13	0.10	
	Y						0.18
RIG	Y*	0.26	0.25	0.27	0.23	0.19	
	EBV	0.13	0.13	0.13	0.13	0.09	
	DEBV	0.14	0.14	0.14	0.14	0.11	
EBV accuracy							
	Y						0.17
RFI	Y*	0.22	0.24	0.26	0.25	0.24	
	EBV	0.18	0.18	0.18	0.19	0.15	
	DEBV	0.18	0.16	0.15	0.14	0.15	
	Y						0.23
DMI	Y*	0.25	0.23	0.23	0.21	0.24	
	EBV	0.23	0.23	0.23	0.23	0.25	

	DEBV	0.14	0.13	0.19	0.18	0.25	
	Y						0.07
FE	Y*	0.12	0.15	0.11	0.13	0.07	
	EBV	0.12	0.10	0.08	0.10	0.05	
	DEBV	0.06	0.07	0.07	0.07	0.05	
	Y						0.08
FCR	Y*	0.13	0.16	0.13	0.08	0.11	
	EBV	0.05	0.10	0.09	0.09	0.09	
	DEBV	0.07	0.13	0.07	0.08	0.09	
	Y						0.14
RG	Y*	0.17	0.16	0.12	0.15	0.12	
	EBV	0.18	0.12	0.13	0.13	0.14	
	DEBV	0.12	0.13	0.13	0.13	0.14	
	Y						0.14
RIG	Y*	0.13	0.11	0.13	0.13	0.18	
	EBV	0.11	0.14	0.12	0.15	0.12	
	DEBV	0.11	0.11	0.10	0.11	0.12	

871 ssGBLUP: single-step genomic best linear unbiased prediction; BLASSO: bayesian least absolute
872 shrinkage and selection operator; Y: phenotype; Y*: adjusted phenotype; EBV: estimated breeding
873 value; DEBV: deregressed estimated breeding value

874 **Table 5** *Phenotype and pseudo-phenotype regression coefficient on genomic*
875 *breeding value with their respective p-values for residual feed intake (RFI), dry matter*
876 *intake (DMI), feed efficiency (FE), feed conversion ratio (FCR), residual body weight*
877 *gain (RG) and residual intake and body weight gain (RIG) in Nelore cattle using*
878 *different models and validation approaches*

Trait	Pseudo-phenotype	Bayes A	Bayes B	Bayes Cπ	Blasso	Bayes R	ssGBLUP
Random							
RFI	Y						1.081 (0.001)
	Y*	1.026 (0.001)	1.033 (0.001)	1.043 (0.001)	1.024 (0.001)	1.026 (0.001)	
	EBV	1.057 (0.001)	1.044 (0.001)	1.045 (0.001)	1.053 (0.001)	1.057 (0.001)	
	DEBV	1.049 (0.001)	1.071 (0.001)	1.058 (0.001)	1.075 (0.001)	1.049 (0.001)	
DMI	Y						1.082 (0.001)
	Y*	1.046 (0.001)	1.000 (0.003)	0.997 (0.002)	1.041 (0.001)	1.046 (0.001)	
	EBV	1.062 (0.001)	1.015 (0.003)	1.019 (0.002)	1.031 (0.001)	1.062 (0.001)	
	DEBV	1.062 (0.001)	1.015 (0.002)	1.047 (0.001)	1.051 (0.001)	1.050 (0.001)	
FE	Y						1.072 (0.001)
	Y*	1.021 (0.001)	1.058 (0.001)	1.029 (0.001)	1.095 (0.001)	1.021 (0.002)	
	EBV	1.057 (0.001)	1.081 (0.001)	1.069 (0.001)	1.048 (0.001)	1.057 (0.001)	
	DEBV	1.057 (0.001)	1.081 (0.001)	1.056 (0.001)	1.045 (0.001)	1.033 (0.001)	
FCR	Y						1.064

							(0.001)
		Y*	1.043 (0.001)	1.094 (0.001)	1.059 (0.001)	1.071 (0.001)	1.043 (0.001)	
		EBV	1.078 (0.001)	1.058 (0.001)	1.028 (0.003)	1.027 (0.001)	1.078 (0.001)	
		DEBV	1.078 (0.001)	1.058 (0.001)	1.014 (0.002)	1.044 (0.001)	1.041 (0.001)	
		Y						1.062 (0.001)
	RG	Y*	1.091 (0.001)	1.064 (0.001)	1.053 (0.001)	1.071 (0.001)	1.091 (0.001)	
		EBV	1.062 (0.001)	1.044 (0.001)	1.075 (0.001)	1.072 (0.001)	1.069 (0.001)	
		DEBV	1.069 (0.001)	1.044 (0.001)	1.043 (0.001)	1.071 (0.001)	1.074 (0.001)	
		Y						1.046 (0.001)
	RIG	Y*	1.103 (0.003)	1.056 (0.001)	1.088 (0.001)	1.074 (0.001)	1.103 (0.001)	
		EBV	1.059 (0.001)	1.036 (0.001)	1.027 (0.003)	1.055 (0.001)	1.059 (0.002)	
		DEBV	1.059 (0.001)	1.036 (0.002)	1.067 (0.001)	1.040 (0.001)	1.055 (0.001)	
Age								
		Y						1.073 (0.001)
	RFI	Y*	0.980 (0.003)	1.090 (0.001)	1.020 (0.001)	0.940 (0.002)	1.120 (0.001)	
		EBV	1.140 (0.001)	1.120 (0.001)	1.070 (0.001)	1.110 (0.001)	1.080 (0.001)	
		DEBV	1.160 (0.001)	1.110 (0.001)	1.120 (0.001)	1.080 (0.001)	1.120 (0.001)	
	DMI	Y						1.023 (0.001)
		Y*	0.960	0.960	0.970	0.960	1.030	

		(0.002)	(0.003)	(0.002)	(0.002)	(0.001)	
	EBV	1.160	1.180	1.120	1.170	1.090	
		(0.001)	(0.001)	(0.001)	(0.001)	(0.001)	
	DEBV	1.150	1.120	1.060	1.140	1.120	
		(0.001)	(0.001)	(0.001)	(0.001)	(0.001)	
	Y						1.133
							(0.001)
	Y*	0.950	1.060	1.010	0.920	1.150	
FE		(0.002)	(0.001)	(0.001)	(0.002)	(0.001)	
	EBV	1.070	0.950	1.190	1.120	0.960	
		(0.001)	(0.001)	(0.001)	(0.001)	(0.001)	
	DEBV	1.080	0.990	1.060	0.960	1.090	
		(0.001)	(0.002)	(0.001)	(0.001)	(0.001)	
	Y						1.050
							(0.001)
	Y*	1.030	0.980	1.070	0.990	1.040	
FCR		(0.001)	(0.002)	(0.001)	(0.002)	(0.001)	
	EBV	1.180	1.190	0.980	1.190	1.090	
		(0.001)	(0.001)	(0.002)	(0.001)	(0.001)	
	DEBV	1.040	1.070	1.030	1.190	1.020	
		(0.001)	(0.001)	(0.002)	(0.001)	(0.002)	
	Y						1.117
							(0.001)
	Y*	1.040	0.930	1.040	0.950	1.060	
RG		(0.001)	(0.002)	(0.002)	(0.002)	(0.001)	
	EBV	1.080	1.050	1.130	1.090	1.060	
		(0.001)	(0.001)	(0.001)	(0.001)	(0.001)	
	DEBV	1.090	1.020	1.050	0.960	1.020	
		(0.001)	(0.002)	(0.001)	(0.002)	(0.002)	
	Y						1.057
							(0.001)
	Y*	0.940	1.060	0.980	1.030	1.090	
RIG		(0.002)	(0.001)	(0.002)	(0.001)	(0.001)	
	EBV	1.170	1.120	1.100	1.070	0.960	
		(0.001)	(0.001)	(0.001)	(0.001)	(0.002)	

	DEBV	1.090 (0.001)	0.910 (0.003)	0.940 (0.002)	0.930 (0.003)	1.040 (0.001)	
EBV accuracy							
	Y						1.073 (0.001)
RFI	Y*	1.090 (0.001)	0.910 (0.003)	0.940 (0.002)	0.930 (0.002)	1.040 (0.001)	
	EBV	1.150 (0.001)	1.120 (0.001)	1.030 (0.002)	1.020 (0.002)	0.940 (0.002)	
	DEBV	1.080 (0.001)	1.120 (0.001)	1.150 (0.001)	1.130 (0.001)	1.090 (0.001)	
	Y						1.097 (0.001)
DMI	Y*	1.070 (0.001)	1.040 (0.001)	1.060 (0.001)	1.040 (0.001)	1.060 (0.001)	
	EBV	0.920 (0.002)	1.090 (0.001)	1.060 (0.001)	1.090 (0.001)	0.960 (0.002)	
	DEBV	0.950 (0.002)	0.960 (0.002)	1.050 (0.001)	1.190 (0.001)	1.090 (0.001)	
	Y						1.113 (0.001)
FE	Y*	1.040 (0.001)	1.010 (0.001)	1.030 (0.002)	0.950 (0.002)	1.130 (0.001)	
	EBV	0.910 (0.002)	1.010 (0.001)	1.030 (0.001)	0.980 (0.002)	1.100 (0.001)	
	DEBV	1.120 (0.001)	1.160 (0.001)	1.120 (0.001)	1.160 (0.001)	1.120 (0.001)	
	Y						1.090 (0.001)
FCR	Y*	1.050 (0.001)	1.010 (0.002)	1.030 (0.001)	1.030 (0.001)	1.010 (0.002)	
	EBV	1.060 (0.001)	1.090 (0.001)	1.040 (0.001)	1.010 (0.002)	1.050 (0.001)	
	DEBV	1.150 (0.001)	1.130 (0.001)	0.910 (0.002)	1.090 (0.001)	1.060 (0.001)	

RG	Y						1.127 (0.01)
	Y*	0.910 (0.002)	0.950 (0.002)	1.090 (0.001)	1.080 (0.001)	1.040 (0.002)	
	EBV	1.090 (0.001)	1.050 (0.001)	1.060 (0.001)	1.040 (0.002)	1.080 (0.001)	
	DEBV	1.140 (0.001)	1.130 (0.001)	0.910 (0.002)	1.150 (0.001)	1.170 (0.001)	
RIG	Y						1.70 (0.001)
	Y*	1.010 (0.003)	1.040 (0.001)	1.020 (0.002)	1.130 (0.001)	1.080 (0.001)	
	EBV	0.920 (0.002)	1.090 (0.001)	1.080 (0.001)	1.030 (0.002)	1.100 (0.001)	
	DEBV	1.140 (0.001)	0.930 (0.002)	1.160 (0.001)	1.170 (0.001)	1.030 (0.002)	

ssGBLUP: single-step genomic best linear unbiased prediction; BLASSO: bayesian least absolute shrinkage and selection operator; Y: phenotype; Y*: adjusted phenotype; EBV: estimated breeding value; DEBV: deregressed estimated breeding value. [#]Coefficients from regression analyses that were significant in ANOVA at a significance level of 0.05

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Figure captions

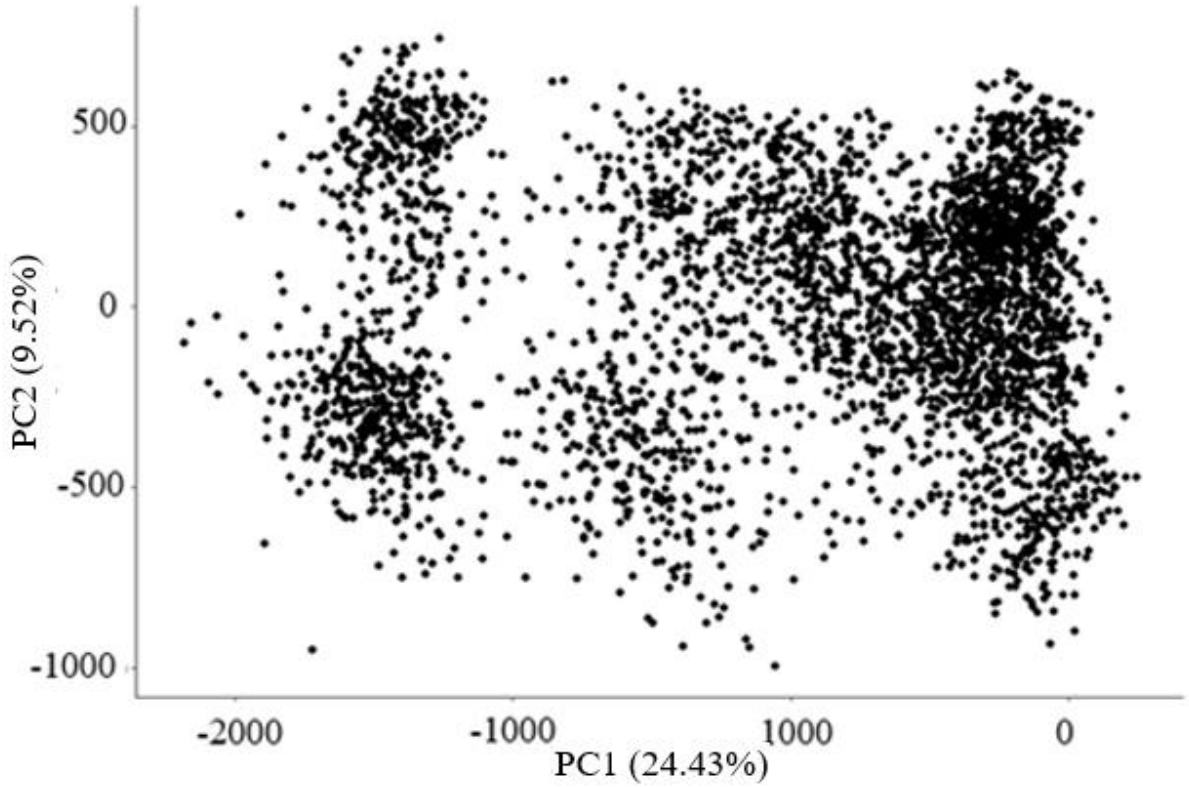

Fig. 1. Principal components (PC) of genomic relationship among Nelore cattle evaluated for feed efficiency related traits.

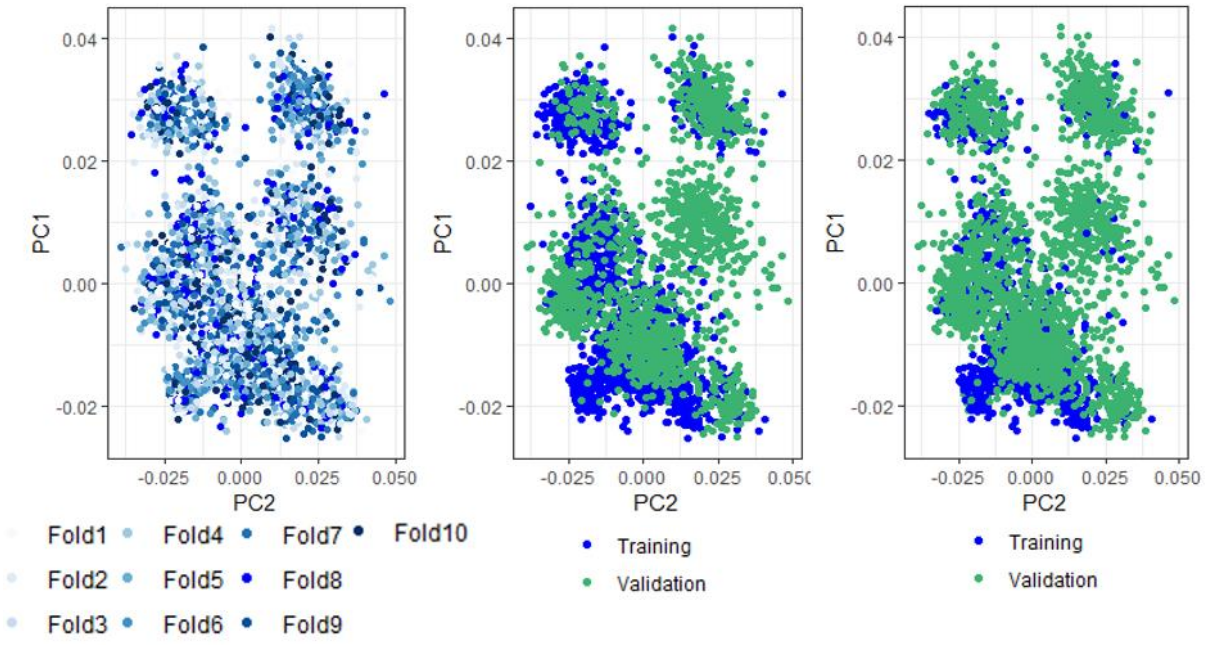

Fig. 2. Distribution of training and validation populations of Nelore cattle for clustering by random (A), age (B) and genetic breeding value accuracy (C) by principal components (PC).

Supplementary Material - Genomic prediction ability for feed efficiency traits using different models and pseudo-phenotypes under several validation strategies in Nelore cattle

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Animal: An International Journal of Animal Bioscience

Supplementary Table S1 – *Mean squared error (MSE) of genomic breeding value prediction for residual feed intake (RFI), dry matter intake (DMI), feed efficiency (FE), feed conversion ratio (FCR), residual body weight gain (RG) and residual intake and body weight gain (RIG) in Nelore cattle using single-step genomic best linear unbiased prediction (ssGBLUP), Bayes A, Bayes B, Bayes Cπ, Bayes R and bayesian least absolute shrinkage and selection operator (BLASSO)*

Trait	Pseudo-phenotype	Bayes A	Bayes B	Bayes Cπ	Blasso	Bayes R	ssGBLUP
Random							
RFI	Y						0.167
	Y*	0.456	0.456	0.457	0.456	0.456	
	EBV	0.010	0.010	0.010	0.010	0.010	
	DEBV	0.030	0.030	0.030	0.030	0.030	
DMI	Y						0.389
	Y*	0.801	0.800	0.800	0.799	0.799	
	EBV	0.021	0.021	0.022	0.021	0.021	
	DEBV	0.087	0.089	0.087	0.087	0.087	
FE	Y						0.010
	Y*	0.013	0.010	0.010	0.010	0.010	
	EBV	0.014	0.011	0.010	0.013	0.013	
	DEBV	0.010	0.010	0.010	0.010	0.010	
FCR	Y						3.618
	Y*	9.275	9.277	9.362	9.281	9.281	
	EBV	0.058	0.059	0.058	0.058	0.058	
	DEBV	0.172	0.172	0.173	0.173	0.173	
RG	Y						0.013
	Y*	0.020	0.020	0.020	0.020	0.020	
	EBV	0.014	0.016	0.010	0.019	0.019	
	DEBV	0.013	0.011	0.010	0.010	0.010	
RIG	Y						0.173
	Y*	0.455	0.436	0.434	0.414	0.414	
	EBV	0.022	0.022	0.022	0.022	0.022	
	DEBV	0.025	0.025	0.025	0.025	0.025	
Age							
RFI	Y						0.107
	Y*	0.270	0.270	0.270	0.270	0.270	

	EBV	0.010	0.010	0.010	0.010	0.010	
	DEBV	0.030	0.040	0.040	0.030	0.040	
DMI	Y						0.327
	Y*	0.560	0.560	0.580	0.960	0.580	
	EBV	0.030	0.030	0.030	0.030	0.030	
	DEBV	0.030	0.110	0.110	0.110	0.110	
FE	Y						0.017
	Y*	0.020	0.020	0.020	0.010	0.010	
	EBV	0.010	0.010	0.010	0.010	0.010	
	DEBV	0.010	0.010	0.010	0.010	0.010	
FCR	Y						3.717
	Y*	7.260	7.240	7.380	7.210	7.180	
	EBV	0.070	0.070	0.070	0.100	0.100	
	DEBV	0.070	0.210	0.210	0.210	0.210	
RG	Y						0.023
	Y*	0.020	0.020	0.020	0.020	0.020	
	EBV	0.010	0.010	0.020	0.020	0.020	
	DEBV	0.010	0.010	0.010	0.010	0.010	
RIG	Y						0.113
	Y*	0.280	0.280	0.280	0.280	0.280	
	EBV	0.030	0.030	0.030	0.030	0.020	
	DEBV	0.030	0.030	0.030	0.030	0.030	
EBV accuracy							
RFI	Y						0.130
	Y*	0.360	0.360	0.360	0.360	0.360	
	EBV	0.020	0.020	0.020	0.020	0.020	
	DEBV	0.050	0.050	0.050	0.050	0.050	
DMI	Y						0.303
	Y*	0.920	0.950	0.900	0.830	0.840	
	EBV	0.030	0.030	0.020	0.030	0.030	
	DEBV	0.100	0.100	0.100	0.100	0.010	
FE	Y						0.013
	Y*	0.010	0.010	0.010	0.010	0.020	
	EBV	0.010	0.020	0.010	0.020	0.010	
	DEBV	0.020	0.020	0.010	0.020	0.010	

FCR	Y						3.700
	Y*	7.260	7.210	7.380	7.280	7.210	
	EBV	0.070	0.070	0.070	0.070	0.030	
	DEBV	0.220	0.220	0.220	0.220	0.220	
RG	Y						0.017
	Y*	0.020	0.020	0.020	0.020	0.020	
	EBV	0.020	0.020	0.020	0.010	0.020	
	DEBV	0.010	0.010	0.010	0.010	0.020	
RIG	Y						0.047
	Y*	0.030	0.030	0.030	0.030	0.020	
	EBV	0.060	0.060	0.050	0.050	0.080	
	DEBV	0.060	0.080	0.080	0.080	0.060	

Y: phenotype; Y*: adjusted phenotype; EBV: estimated breeding value; DEBV: deregressed estimated breeding value.

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CAPÍTULO 4 - Weighted single-step genome-wide association study and pathway analyses for feed efficiency traits in Nelore cattle

Running tittle: Genome-wide association studies for feed efficiency in Nelore cattle

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Abstract: The aim was to conduct a weighted single-step genome-wide association study to detect genomic regions and putative candidate genes related to residual feed intake, dry matter intake, feed efficiency, feed conversion ratio, residual body weight gain, residual intake and weight gain in Nelore cattle. Several protein-coding genes were identified within the genomic regions that explain more than 0.5% of the additive genetic variance for these traits. These genes were associated with insulin, leptin, glucose, protein and lipid metabolisms, energy balance, heat and oxidative stress, bile secretion, satiety, feed behavior, salivation, digestion and nutrient absorption. Enrichment analysis revealed functional pathways (P-value <0.05) such as neuropeptide signaling (GO:0007218), negative regulation of canonical Wingless Int-1 (Wnt) signaling (GO:0090090), bitter taste receptor activity (GO:0033038), neuropeptide hormone activity (GO:0005184), bile secretion (bta04976), taste transduction (bta0742), and glucagon signaling pathway (bta04922). The identification of these genes, pathways and their respective functions should contribute to a better understanding of the genetic and physiologic mechanisms regulating Nelore feed efficiency related traits.

Keywords: *Bos indicus*, residual body weight gain, residual feed intake, weighted single-step, GBLUP

Introduction

In beef cattle, the most costly component is the feedstuff, which have increased significantly in the last years reducing the beef cattle operation profitability (Boaitey, Goddard, Mohapatra, & Crowley, 2017). Approximately 65 to 70% of the metabolizable energy required for beef production is used to meet maintenance requirements (Ferrell & Jenkins, 1985). Although *Bos indicus* cattle has less maintenance requirements per kilogram of metabolize weight than *Bos taurus* (Sainz, Barioni, Paulino, Valadares Filho, & Oltjen, 2006), decreasing

the feedstuff costs involves reducing the maintenance requirement (Ferrell & Jenkins, 1985). The livestock has been recognized as one of those responsible for environmental impacts due to manure and gas production (Boaitey et al., 2017). These facts make feed efficiency an economically relevant trait to improve the profitability and reduce the environmental impact (Boaitey et al., 2017).

To increase the efficiency in converting food into carcass components, the residual feed intake (RFI), residual body weight gain (RG) and, the combination of these two traits, residual intake and body weight gain (RIG) were proposed (Berry & Crowley, 2012). These traits were low genetic correlated with adult weight and carcass composition, different from reported for feed conversion ratio (FCR) and feed efficiency (FE) (Berry & Crowley, 2012; Koch, Swiger, Chambers, & Gregory, 1963; Olivieri et al., 2016; Santana et al., 2014). Thus, RFI, RG and RIG are preferred measures for dissecting the under-lying biology related to feed efficiency (Seabury et al., 2017).

Complex genetic background and physiology of the feed efficiency related traits limits the understanding of the mechanisms involved in phenotypic expression and identification of more efficient animals regarding feed utilization (Rolf et al., 2012). Several studies identified biological and genetic mechanisms that could explain the differences in beef-cattle feed efficiency (Gomes et al., 2013; Olivieri et al., 2016; Rolf et al., 2012; Santana et al., 2014; Seabury et al., 2017). One of the main mechanisms that lead to variation in feed efficiency is the maintenance requirement, which is related to the animal's energy expenditure and the ability to increase the carcass weight (Ferrell & Jenkins, 1985). Although this information is valuable, is still insufficient to elucidate all mechanisms that affect the phenotypic feed efficiency expression (Gomes et al., 2013; Olivieri et al., 2016; Rolf et al., 2012; Santana et al., 2014; Seabury et al., 2017). The development of electronic technologies that allow the automatically measurement of individual feed intake and new evaluation traits, led to easier phenotype

collection and evaluation of feed efficiency in beef cattle, which is an expensive measurement phenotype (Boaitey et al., 2017). Up to date, there is a low number of records collected for feed efficiency related traits in Zebu cattle (Olivieri et al., 2016; Santana et al., 2014).

The genomic information can be applied in genome-wide association studies (GWAS), which is a relevant methodology that can be applied under different statistical-computational tools and allow the identification of genes and genomic regions that explain part of the genetic variance for the evaluated traits (Olivieri et al., 2016; Rolf et al., 2012; Santana et al., 2014). In livestock, several genomic regions with small effects and a large number of quantitative trait loci (QTL) was identified through GWAS (H. Wang, Misztal, Aguilar, Legarra, & Muir, 2012; Webber, 2011; Yang, Lee, Goddard, & Visscher, 2013). The phenotype expression is a result of complex interactions among genes and multiple regulatory mechanisms. Enrichment analyses can be used to identify the functions of genes and complement the GWAS results. This information elucidates the biological mechanisms and genetic architecture involved in phenotypic expression of feed efficiency related traits, since these traits are of complex nature and controlled by several QTLs with small effect (Olivieri et al., 2016; Rolf et al., 2012; Santana et al., 2014a; Seabury et al., 2017). However, most of the GWAS studies for feed efficiency in Zebu breeds were performed with experimental populations or low number of herds with small sample size (Olivieri et al., 2016; Rolf et al., 2012; Santana et al., 2014). Thus, additional studies with larger sample size under different conditions are necessary to increase the knowledge about the genetic background of feed efficiency related traits in Zebu cattle under tropical conditions.

The aim of this study was to conduct a weighted single-step genome-wide association study (WssGWAS) to detect genomic regions and putative candidate genes related to feed efficiency related traits in Nelore cattle. In addition, gene set enrichment analysis was

performed to better understand the biological processes and pathways shared by feed efficiency trait-associated genes.

Material and methods

Ethics statement

The research project was approved by the Committee on Ethics in the Use of Animals (CEUA/PRPI) of the Federal University of Goiás (UFG), according to protocol N° 088/18 issued by this institution.

General data information

Data from 4,329 animals tested for feed efficiency, carried out between 2011 and 2018, and genotypic information from 3,594 animals were considered and provided by the Nelore Brazil Breeding Program, coordinated by the National Association of Breeders and Researchers (ANCP). Animals belonged to 39 farms located in the Midwest, Southeast, Northeast and North regions of Brazil. The relationship matrix used in the analyses was calculated based on pedigree information from 58,374 animals with 6,309 sires and 37,147 dams through nine generations. The animals that composed the dataset had an average inbreeding of 0.071%, and the proportion of inbreeding was 0.41% over the total population. These parameters were estimated using the INBUPGF90 program (Misztal, 2017).

A total of 125 feed efficiency tests were performed to assess the feed efficiency related traits. The animals were evaluated in feedlot with an average age of 13.5±3.92 months at the beginning of the tests under similar management and environmental conditions. The tests were conducted using the same protocol (Mendes et al., 2020) in three ranches (HoRa Hofig Ramos, Rancho da Matinha and AgroNova) and two research centers (Embrapa Rice and Beans and

Federal University of Uberlandia). Even though the diets offered over the years differed in composition and ingredients, they were formulated based on silage and commercial concentrate, with an average of 64% total digestible nutrients, 13% crude protein, 76% dry matter and formulated for gains of 1.2 kg/day (Mendes et al., 2020).

During the tests, the average weight of each animal was obtained by periodic weighing, as well as at the beginning and end of the evaluation period. Forage, concentrate and wastes samples were collected every week to evaluate chemical composition.

DNA samples were obtained from hair follicles taken from animals' tails and placed in card with adhesive film. The animals were genotyped for SNPs markers using CLARIFIDE® Nelore 3.1 low-density panel, containing approximately 29,000 SNP markers. DNA extraction and sample genotyping were performed by Zoetis® (Kalamazoo, MI), through its protocol.

Performance traits

The feed efficiency traits were estimated within each contemporary group (GC). The CG was composed by farm, management group, feed efficiency test, sex, year and birth season (dry season from April to September and the wet season from October to March). The effects included in the CG were those whose significance value was <0.001 obtained in ANOVA results.

The DMI was measured by collective stalls equipped with automated systems (GrowSafeSystem® and Intergado®), for a minimum of 70 days preceded by adaptation. The DMI, measured in kg/day, was obtained by calculating the average of all valid daily intake values during the test period. As quality control, daily DMI records within ±3.5 standard deviations from the average daily DMI of the contemporary group were considered in the analysis. Additionally, daily DMI obtained on days with a power outage or weighing scale adjustments were excluded from the analysis. The DMI was calculated as the amount of

individually consumed feed automatically recorded by the electronic systems (GrowSafeSystem® and Intergado®) (Mendes et al., 2020).

To estimate RFI and RG, ADG and metabolic body weight ($MW^{0.75}$) were calculated. ADG (kg/day) was estimated by the linear regression coefficient of the weights as a function of the days in test (DIT), using the *lm* function of R program (2018) and the following equation:

$$y_{ij} = \alpha_i + \beta_i * DIT_j + \varepsilon_{ij}$$

where: y_{ij} is the weight of i[th] animal; α_i is the intercept of the regression equation which represents the initial weight; β_i is the linear regression coefficient which represents the ADG; DIT_j is the day in the performance test of j[th] observation, and; ε_{ij} is the residual associated to each observation. It was assumed that the residues were independent and not correlated and residual effects were normally distributed with mean zero. The $MW^{0.75}$ was given from body weight and ADG:

$$MW_i^{0.75} = \left[\alpha_i + \beta_i * \left(\frac{DIT_j}{2}\right)\right]^{0.75}$$

where: $MW_i^{0.75}$ is the metabolic weight of i[th] animal; α_i is the intercept of the regression equation which represents the initial weight; β_i is the linear regression coefficient which represents the ADG, as described and obtained above in estimating ADG.

FE, measured in kg ADG/kg DMI, was obtained as the ratio between ADG and DMI. FCR, measured in kg DMI/kg ADG, was obtained by the inverse ratio (DMI/ADG). RFI (kg of DM/day) was estimated, within each CG, by the residual of the DMI regression as a function of ADG and $MW_i^{0.75}$, using the R program (2018) and the equation (Koch et al., 1963):

$$y_i = \beta_o + \beta_1 ADG + \beta_2 MW_i^{0.75} + \varepsilon\ (RFI)$$

where: *y* is individual dry matter intake of i[th] animal; β_o is the intercept; β_1, and β_2 are the linear regression coefficient of ADG and $MW_i^{0.75}$, respectively; and ε is the residual error, i.e. RFI. It was assumed that the residues were independent and not correlated and residual effects were

normally distributed with mean zero (Sen & Sen, 2014). Regression analysis was performed and no effect of backfat thickness (BF) on RFI was observed, thus the RFI was not adjusted for fat thickness.

The RG (Berry & Crowley, 2012; Koch et al., 1963) (kg of ADG/day) was obtained as the difference between the observed ADG and the estimated based on DMI and $MW^{0.75}$. The estimated average daily gain (ADGe) was obtained using the *lm* function on the R program (2018), within CG and by:

$$ADG_{ei} = \beta_o + \beta_1 DMI + \beta_2 MW_i^{0.75} + \varepsilon\ (RG)$$

where: β_0 is the intercept, β_1, and β_2 are the regression coefficients of DMI and $MW_i^{0.75}$, respectively; and ε is the residual error, i.e. RG. It was assumed that the residues were independent and not correlated and residual effects were normally distributed with mean zero (Sen & Sen, 2014).

RIG was calculated as RG-RFI, after standardizing both traits to a variance of 1, allowing of their combination into single value (Berry & Crowley, 2012). Both traits, RFI and RG, are linear functions of their component traits: DMI, ADG, and $MW^{0.75}$. The number of records and descriptive statistics for the evaluated traits are summarized in Table 1.

Statistical and quality control analyses

Records within ±3.5 standard deviations from the CG mean were considered in the analysis. Additionally, all CG should have at least four animals in order to proceed with the analysis. In the quality control (QC) for genomic data, SNPs with minor allele frequency (MAF), call rate and p-value for Hardy-Weinberg equilibrium test (HWE) less than 0.02; 0.95 and 0.15, respectively, were excluded. Only SNPs in autosome chromosomes and with known position according to UMD 3.1 bovine genome were considered. Samples with call rates below to 0.95 were excluded from the analysis. This process was performed with R program (2018),

using scripts developed for this purpose, resulting in a data set with 19,602 SNP and 3,467 animals.

To evaluate the existence of population substructure a principal component analyses (PCA) was performed using information from SNPs and genomic relationship matrix of individuals (VanRaden, 2008) (Appendice - Figure 1). The proportion of variance explained by the two first principal components was 33.95%. The PC1 e PC2 did not group the animals into clear-cut clusters, implying that genetic admixture probably existed for the evaluated population. The animals' dispersion in the PCA plot indicated the absence of subgroups among the evaluated animals, since there is no formation of major components.

The genetic distance between individuals was calculated based on their genotypes using the method Jukes-Cantor (Jukes & Cantor, 1969) and R program (2018). The genetic distances values were, on average, 0.08 (0.0 to 0.1816), indicating that the data are not dispersed or sub-grouped in whole population (Table 2).

Weighted single-step genome-wide association studies

The model to perform the WssGWAS included the direct additive genetic and residual effects as random effects, and the CG was included as a fixed effect and animal's age as covariable (linear effect). The variance components necessary to perform the WssGWAS analysis were estimated by single-trait analyses (Brunes et al., 2020), through the restricted maximum likelihood method, with REMLF90 program (Misztal, 2017) and using single-step genomic approach (Aguilar et al., 2010). The variance components and heritability estimates obtained by Brunes et al. (2020) are summarized in Table 1.

The effects and variances of SNPs were estimated by the Weighted single-step genome-wide association study proposed by H. Wang et al. (2012), using the BLUPF90 adapted for

genomic analyses (Misztal, 2017). The WssGWAS uses matrix H^{-1} (Aguilar et al., 2010), that combining pedigree and genomic information:

$$H^{-1} = A^{-1} + \begin{bmatrix} 0 & 0 \\ 0 & G^{-1} - A_{22}^{-1} \end{bmatrix}$$

where, G^{-1} is the inverse of genomic relationship matrix; A^{-1} is the inverse of additive relationship matrix; and A_{22} is the inverse pedigree relationship matrix for genotyped animals**.** The genomic matrix (G) was created as follows (VanRaden, 2008):

$$G = \frac{ZDZ'}{\sum_{i=1}^{M} 2p_i(1-p_i)}$$

Where, Z is an incidence matrix adjusted for allele frequencies; D is a diagonal matrix of weights for SNP variances; M is the number of markers, and p_i represented the minor allele frequency of the i[th] SNP. The SNP effects and weights for WssGWAS were calculated iteratively as follows (H. Wang et al., 2012):

1. Set $t = 1, \boldsymbol{D}_{(t)} = \boldsymbol{I}; G_{(t)} = \boldsymbol{\lambda Z D}_{(t)}\boldsymbol{Z'}$

$$\lambda = \frac{1}{\sum_{i=1}^{M} 2p_i(1-p_i)}$$

2. Estimate GEBV for all animals using ssGBLUP approach;

3. Compute SNP effects as $\hat{u}_{(t)} = \lambda D_{(t)} Z' \, G_{(t)}^{-1 \hat{\alpha}_g}$, where $\hat{u}_{(t)}$ was a vector of the SNP effects estimation and $\hat{\alpha}_g$ is the GEBV of animals that were also genotyped;

4. Calculate SNP weights for the next iteration using $d_{i(t=1)} = \hat{u}_{i(t)}^2 2p_i(1-p_i)$

where *i* is the *i*[th] SNP;

5. The SNP weights were normalized to keep the total genetic variance constant:

$$D_{(t+1)} = \frac{tr(D_{(t)})}{tr(D_{(t+1)})} D_{(t+1)}$$

6. Calculate $G_{(t+1)}$

$$G_{(t+1)} = \frac{ZD_{(t+1)}Z'}{\sum_{i=1}^{M} 2p_i(1-p_i)}$$

7. $t = t + 1$;

8. Exit, or loop to step 2 or 3 until the stabilization of the SNP weighted estimates.

This procedure was run for four iterations. At each iteration, the weights for SNPs were updated (steps 4 and 5), used to construct the G matrices (step 6), update the GEBV (step 2) and, consequently, the estimated SNP effects (step 3). The results were presented for windows with 10 adjacent SNPs (±1 Mb). The window size was defined after analyses performed with R software (2017), in which the average and mode haplotype block was obtained in studied population. In addition, the window size was based on the linkage disequilibrium of Zebu genome (Espigolan et al., 2013). Windows based on the number of the SNPs instead of physical size was chosen in order to avoid biases due to uneven distributed SNPs in the genotype panel. The percentage of genetic variance explained by the i^{th} window was calculated as:

$$\frac{Var(a_i)}{\sigma_a^2} = X\ 100 = \frac{Var(\sum_{j=1}^{10} Z_j \hat{u}_j)}{\sigma_a^2} X\ 100$$

where: a_i is the genetic value of the i^{th} SNP window that consists of a region of 10 adjacent SNPs; σ_a^2 is the total additive genetic variance; Z_j is the vector of gene content of the j^{th} SNP for all individuals, and; $\hat{u}_j$ is the effect of the i^{th} SNP with the i^{th} window. Manhattan plots based on the proportion of additive genetic variance explained by the windows were generated using *qqman* package of R software (2017).

Search for candidate genes and functional enrichment analysis

To determine possible QTLs, genomic regions that explained more than 0.5% of the additive genetic variance were selected. This analyzes were based on WssGWAS for all feed efficiency related traits: RFI, DMI, FE, FCR, RG and RIG. The threshold of 0.5% was chosen

based on the previous reports (R. M. O. Silva et al., 2017; Stafuzza et al., 2019), visual inspection of Manhattan plots, small proportion of explained variance of polygenic traits, and on the expected contribution of SNP windows (Sollero, Junqueira, Gomes, Caetano, & Cardoso, 2017).

For identification and positioning of the selected segments in the bovine genome, a survey was made in the database available using the *Bos taurus* UMD 3.1 genome assembly and Ensembl Biomart tool with Genes 94 database (Haider et al., 2009). The genes content of genomic regions selecting a 500 Kb window around each region (upstream and downstream) were identified. Previous studies also suggested that a similar distance could be used in the GWAS approach to capture the genomic regions affecting quantitative trait in Nelore cattle (Stafuzza et al., 2019), since the average linkage disequilibrium (r^2) is 0.34 in genomic regions within 500 kb length size (Espigolan et al., 2013).

Classification of genes for biological function, metabolic pathway, and gene set enrichment analyses, considering $P < 0.05$ threshold for significance in a Fisher's exact test, were performed with ENSEMBL database and Database for Annotation, Visualization and Integrated Discovery (DAVID) version 6.8 toll (Huang, Sherman, Lempicki, & Lempick, 2009; Huang, Sherman, & Lempicki, 2009), from annotated genes in the Ensembl and to seek for significant clusters.

Results

A total of 14, 15, 21, 22, 26, and 27 genomic regions that explained more than 0.5% of additive genetic variance and harbored genes with known functions associated with RFI, DMI, FE, FCR, RG, and RIG, respectively were identified (Tables 3 to 8 and Figures 1 and 2).

Manhattan Plots (Figures 1 and 2) displayed the genomic regions that explained more than 0.5% of the additive genetic variance for feed efficiency related traits. There were several

genomic regions found on BTA 2, 3, 6, 7, 9, 11, 14, 16, 19, 20, 21, 24, and 29 explaining more than 0.5% of additive genetic variance for more than one evaluated trait (Tables 3 to 8).

A large number of genomic regions explaining more than 0.5% of the additive genetic variance were identified for the studied traits. The genes found in the regions that accounted for more than 0.5% of additive genetic variance and enrichment pathways in each functional category (P <0.05) for feed efficiency related traits are shown in Table 9. The functional enrichment analysis revealed 21 biological processes, 6 molecular functions, 5 cellular components, and 5 KEGG pathways. It was highlighted the following terms related to feed efficiency: neuropeptide signaling pathway (GO:0007218), negative regulation of canonical Wnt signaling pathway (GO:0090090), detection of chemical stimulus involved in sensory perception of bitter taste (GO:0001580), bitter taste receptor activity (GO:0033038), neuropeptide hormone activity (GO:0005184), bile secretion (bta04976), taste transduction (bta0742), and glucagon signaling pathway (bta04922).

Discussion

Several genomic regions with small effect for feed efficiency related traits was also reported in previous studies with Zebu cattle (de Oliveira et al., 2014; Olivieri et al., 2016; Santana et al., 2014). Thus, some small-effect genomic markers contribute to differences in these traits, which may be related to their polygenic architecture (Serão et al., 2013). Several genomic regions explaining more than 0.5% of the additive genetic variance for at least two traits were identified. Genes that could be related to feed efficiency related traits in Nelore cattle, according to their functions were highlighted below.

Hormones like insulin, leptin and glucose affects energy metabolism and, consequently, the feed efficiency, since higher supply and utilization of energy results in divergent animals in terms of feed efficiency (Richardson & Herd, 2004). As an example, RFI is related to the basal

energy needs and differences in growth efficiency. Thus, this trait works as an indicator of metabolic efficiency and energy expenditure, which supports the large number of RFI-associated genes that act on energy, insulin and glucose metabolism (Richardson & Herd, 2004). The same concept may be extrapolated to the other feed efficiency related traits, whereas genes related to processes that constantly demand and expenditure energy were observed associated with all evaluated traits.

Several genes related to insulin metabolism were identified, such as *OSM* (Komori, Tanaka, Senba, Miyajima, & Morikawa, 2014), *NOD2* (Rodriguez-Nunez et al., 2017), *IQGAP2* (Brisac et al., 2016), and *AOC3* (Carpene, Iffiu-Soltesz, Bour, Prevot, & Valet, 2007) genes. The action of insulin-related genes result in differences in the mechanisms of hunger and satiety due to energy homeostasis and growth (Kelly et al., 2011; Nascimento et al., 2015), and in the total energy extracted from food, which may cause variation in weight gain, despite there was no difference in feed intake (Rodriguez-Nunez et al., 2017). Low-RFI animals have a higher sensation of satiety due to insulin signaling (Kelly et al., 2011), and serum concentrations of this hormone can be used as indicators of efficient feed utilization in Nelore cattle (Nascimento et al., 2015).

Some leptin-related genes were identified, such as *LIF* (Beretta, Dhillon, Kalra, & Kalra, 2002), *IAPP* (Muff, Born, & Fischer, 1995), and *STAT3* (Weber et al., 2016) genes. The last gene was reported associated with residual feed intake in Angus cattle (Weber et al., 2016). Neurons of the area postrema are co-activated by *IAPP* and glucagon-like peptide-1, regulating feeding, digestive functions, satiety and gastric emptying (Muff et al., 1995), and feed efficiency indirectly. Leptin influences the action of the alpha-melanocyte-stimulating hormone (α-MSH), which is responsible for satiety, acting on the animals' feeding behavior, appetite and emitting signals that stop the seek for food by the animal. Leptin emits signals through the

central nervous system to elicit changes in feeding behavior, energy balance and nutritional status (Zieba, Amstalden, & Williams, 2005).

Genes related to energy and glucose metabolism, one of the main sources of energy for cattle, was identified, such as *FBXO32* (Cleveland & Evenhuis, 2010), *MAF1* (Cherry et al., 2012), and *AK2* (Burkart, Shi, Chouinard, & Corvera, 2011) genes. The *FBX032* gene was reported related to leanness and fatness traits and enhanced growth efficiency in cattle (A. Wang et al., 2013). Under conditions of nutrient limitation, *MAF1* is associated to reduced fitness, stress sensitivity, altered respiratory metabolism, and decreased sporulation efficiency (Cherry et al., 2012). This pattern may be due to increased O_2 consumption by mitochondrial complex 2 and establish faster phosphorylation homeostasis, reduced caloric intake, and increased energy expenditure, being inefficient metabolically and to transform calories into biomass (Bonhoure et al., 2015). These findings explain reduced intake, lower body fat thickness, and blood glucose and insulin concentrations in low-RFI animals. These mechanisms can be ceasing their intake in less time, because they achieve satiety first (Kerley, 2010).

The association of oxidative stress-related genes and feed efficiency occurs because oxidative stress can decrease energetic efficiency as oxidation products that must be degraded by processes such as the ATP-dependent ubiquitin system that needs energy (Bottje & Kong, 2013). This association is due to physiological responses to stress, which include increased metabolic rate and energy expenditure, as well as increased catabolic processes (increased lipolysis and protein degradation) (Iqbal et al., 2005). Thus, higher tolerance for oxidative stress may lead to lower energy expenditure and greater tissue accretion, which may partially explain differences in feed efficiency (Arthur & Herd, 2008). Seen in these terms, *HSF1* (Ebrahimi et al., 2015), *MSH6* and *MSH2* (Lindholm-Perry et al., 2017) genes related to stress response were identified. Indeed, Lindholm-Perry et al. (2017) observed a difference in transcript abundance of *MSH2* among beef cattle with low gain-high intake phenotype.

Zinc is a structural element in protein and is essential for several biochemical and cellular pathways, characterized by coordination and stabilization of one or more zinc ions in several ionic exchange process, participates in DNA and RNA synthesis, cell division and activation, and is indispensable for immune response (Klug & Rhodes, 1987). In addition, zinc finger proteins were reported associated with DMI, FE, and ADG in Nelore cattle (Olivieri et al., 2016; Santana et al., 2014). Indeed, genes as *ZHX1* and *ZHX2* are zinc finger member family and were related to average daily gain in cattle (Serão et al., 2013).

The association of protein metabolism and feed efficiency can be attributed to the energy expenditure from the turnover of body proteins, which can reach 30% of the maintenance energy (Carvalho et al., 2019; Richardson & Herd, 2004). High-RFI animals presented higher levels of protein catabolism or less efficient mechanism of protein utilization, identified by the highest concentration of total plasma protein, blood urea, and aspartate amino transferase (Richardson & Herd, 2004). As a result, higher protein turnover nutrient use efficiency, resulting in different energy expenditures. In this way, it were found *POLR2K, PDE6D, HDDC3* and *POLR2B* genes that play roles in purine metabolism pathways and the *PAICS* and *PPAT* genes that play a role in purine biosynthesis (Cheung et al., 2019; Y. Liu et al., 2008).

Similar to other physiological mechanisms, such as insulin, stress and protein metabolism, the key point of the association between feed efficiency and lipid metabolism is energy expenditure. In general, to deposit fat, cattle needs more energy than to deposit protein, thus protein synthesis is energetically more efficient than fat synthesis. As a result, variations in weight gain and body composition influence the efficiency of nutrient utilization (Arthur & Herd, 2008), often reflecting on fat thickness in the carcass (Basarab et al., 2003).

The reduced lipid synthesis and fat accumulation in high gain-low intake animals may be an indication of energy prioritization away from lipid deposition and towards lean growth or maintaining better health or function of organs (Mukiibi et al., 2018). In these sense, more

efficient animals have lower levels of triacylglycerol, indicating increased mobilization of this lipid to be used as an energy source and to supply the requirement for lean meat deposition that is higher in these animals (Duarte, 2018). This biological mechanism is also related to insulin response (Richardson & Herd, 2004), which supports the relationship between insulin-genes and feed efficiency, as previously stated. Indeed, several lipid-related genes were identified, such as *SDCBP* (Santos, 2018), *ACLY* (Ji, Osorio, Drackley, & Loor, 2012), *OLR1* (Vinsky, Islam, Chen, & Li, 2013), *CRTC3* (Raza et al., 2019), *PRKDC* (Horodyska, Hamill, Varley, Reyer, & Wimmers, 2017), *HNRNPA3* (G. Wang et al., 2018), *HTATIP2* (Liao et al., 2014), and *NFE2L2* (Wu, Cui, & Klaasen, 2011) genes. The *OLR1* and *CRTC3* genes were reported associated with body weight, rib eye area and fat thickness in Nelore (Fonseca et al., 2015), and fat deposition in Qinchuan cattle (Raza et al., 2019), respectively. The *SDCBP* and *NFE2L2* genes were reported associated with RFI (Santos, 2018) and FE (Lima, 2019) in Nelore cattle, respectively.

Mechanisms associated with feed digestives processes affect the intake capacity, absorption process and also the utilization of nutrients by animals (Arthur & Herd, 2008; Richardson & Herd, 2004). Salivation is associated with ruminal motility and function, food passage rate, digestive disorders (Carter & Grovum, 1990). In agreement, *EPCAM* (Mignon-Grasteau et al., 2015), *ATP6V0A1* (Kern et al., 2016), and *RFX6* (Freeman et al., 2010) genes that act on digestive processes and salivation were identified. The *ATP6V0A1* and *RFX6* genes were reported associated with feed efficiency divergent beef steers (Kern et al., 2016) and with DMI in Nelore cattle (Olivieri et al., 2016), respectively.

Regarding to pathway identified by gene set enrichment analyses, some of them and the main genes within metabolic and/or functional pathways related to feed efficiency traits or with functions that may be associated with the phenotypic expression of the evaluated traits were discussed below.

Several genes were identified as related to neuropeptide signaling pathway (GO:0007218) and neuropeptide hormone activity (GO:0005184). The neuropeptide signaling pathway (GO:0007218) was associated with growth and feed utilization traits of Japanese Black cattle (Okada et al., 2018), suggesting that this pathway may affect feed efficiency. Among the genes harbored in these pathways, we highlighted the *PYY, HCRT, HCRTR, NMB, MLNR, NPBWR1*, *PPY, SPX, OPRK1,* and *PENK* genes, which are related to feeding behavior, satiety, and amount of food consumed (Arora, 2006; Hoggard, Bashir, Cruickshank, Miller, & Speakman, 2007; Martín-García et al., 2011; McGregor, Wu, Barber, Ramanathan, & Siegel, 2011; Tyree, Borniger, & Lecea, 2018; Reid et al., 2017; Reyes-Alcaraz et al., 2016; Sakuraia, 2013; Takahashi, Rikimaru, Komatsu, Uemoto, & Suzuki, 2014; Xu et al., 2013).

The *PYY* gene acts as feeding-promotion and feeding-suppression by the hypothalamus, send signals to the central nervous system and regulate functions of the gastrointestinal tract, appetite regulation and feed intake (Arora, 2006). The *NMB* gene action is closely associated with feed efficiency since it represents a mediator between the gut and the brain and serves as a satiation signal to terminate meals and indicating energy balance, reflecting the nutritional status and regulating feed intake over a longer term (Hoggard et al., 2007). The *SPX* gene was implicated in the appetite regulation, feed intake, satiety factor, leptin signaling and related metabolic processes (Reyes-Alcaraz et al., 2016). This gene was acting by inhibiting feed intake via a drop in feed-seeking behavior with an increase in feed rejection activity (Wong et al., 2013). The actions of these genes modulate the animal's nutritional status, feed behavior and intake, thus may lead to obtaining divergent animals for feed efficiency.

The *HCRT* and *PPY* genes have shown a change in circulation within minutes to hours after feeding (Graaf, Blom, Smeets, Stafleu, & Hendriks, 2004; Reid et al., 2017; Tyree et al., 2018). The action of these genes are mediate via leptin and insulin, leading to sensation satiety

and acting in feed intake, energy homeostasis and balance (Graaf et al., 2004; Reid et al., 2017; Tyree et al., 2018).

The *OPRK1* gene mediates stress responses, cortisol response, salivation regulation, and opioid receptor activity (Xu et al., 2013). Also as part of the opioid system (B. M. P. de Silva, 2018), the *PENK* gene is involved in behavior responses and has a role in the feeding behavior of mice (Martín-García et al., 2011). Changing opioid levels alters feed behavior, intake, and efficiency through action on the central nervous system and related to different physiological functions (Glass, Billington, & Levine, 2000).

The glucagon signaling pathway (bta04922) is a involved in energy homeostasis and leaded to suppression of feed intake and behavior, besides being act in the sign of satiety (Inokuchi, Oomura, & Nishimura, 2007). Glucagon is secreted when the animal feeds on a protein-rich diet and promotes protein synthesis (Hentze, Carlsson, Kondo, Nassel, & Rewitz, 2015). This mechanism may be important for growth, lean mass and feed efficiency. The glucagon signaling pathway was identified as a significant overrepresented pathway for intramuscular fat content and fatty acid composition in *Longissimus dorsi* muscle of Simmental and Yunling cattle (H. Zhang et al., 2018).

Among the genes harbored in this pathway, the *SLC2A2*, *G6PC* (Foote, Keel, Zarek, & Lindholm-Perry, 2017), and *PHKB* (Nadeau et al., 2012) genes are related to glucose, insulin and energy metabolism. The *SLC2A2* gene was reported associated with weight gain under the same feeding conditions due to more efficient at small intestinal starch digestion in beef steers (Foote et al., 2017). The *G6PC* gene catalyzes the final steps of gluconeogenesis and glycogenolysis, and was expressed in the fasting or in increased glucose demand in cattle, being related to satiety (Foote et al., 2017). The glycolysis, glycogenesis, and glycogenolysis metabolic pathways are related to the energy supply in the body, being activated to generate ATP (Rui, 2014), which may be related to the use of energy from food for conversion to body

weight. The *PHKB* gene was associated with the carbohydrate metabolic process, glycogenolysis regulation, generation of precursor metabolites and energy. *PHKB* action in the energy metabolism occurs because this gene catalyzes the Ca2+ dependent phosphorylation of glycogen phosphorylase in skeletal muscle and stimulates the breakdown of glycogen to ensure a continuous energy supply (Nadeau et al., 2012). This gene was previously suggested as a candidate gene for feed efficiency related traits in Nelore cattle (Oliveira et al., 2014).

The negative regulation of canonical Wnt signaling pathway (GO:0090090), also known as Wnt/β-catenin signaling, was associated with carcass traits in Nelore cattle (Silva-Vignato et al., 2017). Studies showing that this pathway play important role in skeletal muscle homeostasis (von Maltzahn, Chang, Bentzinger, & Rudnicki, 2012) and the adipocyte differentiation (H. Li, Luo, Liu, Yang, & Yang, 2008). Among the genes in this pathway, the *ZNRF3* gene that encodes a zinc finger protein, inhibits adipogenesis, stimulated lipolysis, and affecting energy expenditure (Chen & Wang, 2018), that may influence the animal's response to weight gain as a function of feed intake. The *SOX17* gene plays a role in regulating insulin secretion in response to fasting and feeding, and controls genes that regulate insulin secretion, as *GLP1R* and *GLUT2* (Jonatan et al., 2014).

The GO term detection of chemical stimulus involved in sensory perception of bitter taste (GO:0001580), bitter taste receptor activity (GO:0033038) and taste transduction (bta04742) harbor genes that are proteins co-expressed in distinct subpopulations of taste bud cells of the human gustatory system (Valente et al., 2018). The bitter taste receptors affect the release of anorexigenic gut hormones and inhibiting gastric contractility, that in turn, may regulate appetite, perception affects feed intake and influence production traits, as body weight (Avau et al., 2015; Ribani et al., 2017). To our knowledge, none of the genes in this pathway were previously reported as candidate genes for feed efficiency in cattle; nevertheless, taste

perception affects feed intake and production traits, as body weight (Ribani et al., 2017), and appear to function in feed efficiency phenotype.

The bile secretion pathway (bta04976) is related to diet and acts in solubilization of fats and subsequently increasing absorption (Reshetnyak, 2013), affecting the feed intake and increased weight gain (Parsaie, Shariatmadari, Zamiri, & Khajeh, 2007). Abo-Ismail et al. (2014) identified it as a potential pathway to contributing to variation in feed efficiency traits in crossbred beef cattle. Among the genes harbored in this pathway, the *CYP7A1* (Alexandre, 2015) and *HMGCR* (Mukiibi et al., 2019) genes play a role in cholesterol and lipid metabolism. The *CYP7A1* action was reported differentially expressed for RFI in Nelore cattle (Alexandre, 2015), which may be due to enhancing the absorption of lipids and lipid-soluble nutrients and follows the aim of improving the supply with metabolizable energy (Wooton-Kee et al., 2010). The *HMGCR* were identified associated with ADG and DMI in Angus (Mukiibi et al., 2019). The *KCNN2* gene play a role in activity in calcium/potassium channels (Shakkottai et al., 2001), and feeding motivation (Kommadath, 2012). These physiological process (calcium/potassium channels) are energetically expensive, being *KCNN2* a particularly intriguing candidate gene for feed efficiency as reported by Olivieri et al. (2016) in a GWAS with feed efficiency in Nelore cattle.

Some of the genomic regions, genes and pathways identified in this study were not reported in public databases related to feed efficiency in cattle (Alexandre, 2015; de Oliveira et al., 2014; Gomes et al., 2013; Lindholm-Perry et al., 2017; Lima, 2019; Mujibi et al., 2011; Olivieri et al., 2016; Rolf et al., 2012; Santana et al., 2014; Santos, 2018; Seabury et al., 2017; Serao et al., 2013; B. M. P. de Silva, 2018). Probably, the feed efficiency related traits in Nelore cattle are regulated by different biological mechanisms than other cattle subspecies; and several physiological mechanisms may be behind feed efficiency control in beef cattle. The maintenance requirement is one of the key points in the feed efficiency regulation, and Zebu

cattle have lower maintenance requirement than taurine, reaching up to 20% lower, which normally leads to lower DMI (CSIRO, 1999; Sainz et al., 2006). This difference is related to less fast heat production; less basal metabolism; the smaller size of their organs; more pronounced peripheral fat deposit, to the detriment of the interposed fat deposit; and the more efficient use of energy for maintenance in Zebu cattle than taurine cattle (Paulino, Fontes, Jorge, Pereira, & Gomes Júnior, 1999). These different physiological responses may justify the identification of genomic regions associated with feed efficiency in Nelore that was not reported in taurine cattle. Also, the variation in SNP allele frequencies, linkage disequilibrium of markers between *Bos taurus* and *Bos indicus* and genetic constitution of the population could result in identifying different markers associated with evaluated traits (de Oliveira et al., 2014; Gomes et al., 2013; Mujibi et al., 2011; Olivieri et al., 2016; Rolf et al., 2012; Santana et al., 2014). In addition, the different methods and larger sample size in this study than commonly observed in studies with Nelore cattle may have resulted in variants that had not yet been identified (de Oliveira et al., 2014; Olivieri et al., 2016; Rolf et al., 2012; Santana et al., 2014).

A large number of genomic regions associated with feed efficiency related traits were identified in this study. These results supports the premise that these traits are highly polygenic and have their expression controlled by many QTL with small individual effects on feed efficiency traits. Pathways involved, mainly, insulin, leptin, glucose, protein and lipid metabolism, energy balance, heat and oxidative stress, zinc finger system, bile secretion, satiety, feed behavior, salivation, digestion and absorption of nutrients were identified and are associated with feed efficiency. Understanding of enriched molecular processes, pathways and genes associated feed efficiency related traits will help shed some light on the underlying DNA variants and candidate genes that are associated with a phenotypic expression of these traits. Therefore, the results obtained in this study would support a better understanding the genetic

and physiological mechanisms that determine feed efficiency and would contribute to increase the reliability of genomic evaluation for feed efficiency related traits in indicine cattle.

Conclusion

The genetic architecture for feed efficiency related traits shows a polygenic model of inheritance with several genomic regions with small effects, harboring possible candidate genes for feed efficiency related traits.

The candidate genes identified are involved in insulin, leptin, glucose, protein and lipid metabolism, energy balance, oxidative stress, zinc finger system, bile secretion, satiety, feed behavior, salivation, digestion, and absorption of nutrients were highlighted as candidates for feed efficiency related traits in cattle. The identification of these genes and their respective functions should contribute to a better understanding of the genetic and physiologic mechanisms regulating Nelore feed efficiency related traits. These results would support the selection for these traits, as developing genomic models incorporating and pondering causal variations or by allowing the associated SNPs to be assigned with higher weights in genomic selection, serving as a basis for fine mapping studies, aiming to identify causal mutations for these traits, or incorporating functional SNPs in the development of new SNP chip panels. The associated genotypes that were identified can potentially be used in animal breeding programs to select for feed efficiency within cattle production systems in a tropical environment.

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Conflict of interest statement

The authors declare that they do not have any conflict of interest.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author upon reasonable request. The data are not publicly available due to privacy or legal restrictions, because it belongs a commercial breeding program.

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Table 1. Number of observations (N), phenotypic mean, standard deviation (SD), number of contemporary groups (N° CG), additive genetic variance (σ^2_a), residual variance (σ^2_e) and heritability (h^2 ± standard-error (SE)) for feed efficiency related traits in Nelore cattle.

Trait	N	Mean	SD	N° CG	σ^2_a*	σ^2_e*	h^2±SE*
RFI	4,080	0.00	0.70	125	0.09	0.042	0.17±0.04
DMI	4,097	7.97	1.75	126	0.21	0.68	0.23±0.04
FE	2,242	0.09	0.03	93	0.00030	0.00404	0.07±0.03
FCR	2,235	12.18	4.43	125	0.80	8.14	0.09±0.03
RG	2,056	0.00	0.20	93	0.03	0.16	0.17±0.05
RIG	2,033	0.02	0.74	93	0.11	0.43	0.20±0.05

RFI: residual feed intake; DMI: dry matter intake; FE: feed efficiency; FCR: feed conversion ratio; RG: residual body weight gain; RIG: residual intake and body weight gain. *The variance components were estimated by single-trait analyses in a single-step genomic approach (Brunes et al., 2020).

Table 2. Descriptive analysis of genetic distance in Nelore cattle.

Statistics	Mean	Median	Minimum	Maximum	1° quartile	3° quartile
Whole population	0.0865	0.0835	0.0000	0.1816	0.0526	0.1030
Between folds of random validation	0.0912	0.0971	0.0000	0.1710	0.0421	0.0991
Training and validation population for age approach	0.1161	0.1158	0.0002	0.1816	0.0635	0.1174
Training and validation population for EBV accuracy	0.1095	0.1087	0.0001	0.1796	0.0603	0.1125

Table 3. Genomic regions of 10 adjacent SNPs that explain more than 0.5% of the additive genetic variance (Var) for residual feed intake (RFI) in Nelore cattle.

BTA	Start position (bp)	End position (bp)	Var (%)	Genes
2	20,023,792	21,555,517	1.12830	NFE2L2, HOXD3, HOXD4, HOXD9, HOXD10, ATF2, CHN1
2	120,775,372	122,330,054	1.11169	PDE6D, COPS7B, ALPI, ECEL1, CHRND, CHRNG, EIF4E2, PHC2, A3GALT2, ZNF362, TRIM62, AZIN2, AK2, YARS, RBBP4, ZBTB8A, TSSK3, MARCKSL1, HDAC1, LCK, MTMR9, PTP4A2, SPOCD1, PEF1, TINAGL1
3	54,028,274	54,062,811	0.50873	LRRC8D, LRRC8C, LRRC8B, GBP6, GBP5
5	70,280,639	71,120,972	0.51857	NUAK1, POLR3B, RFX4, RIC8B, BTBD11, PRDM4, ASCL4, RTCB
6	73,547,830	74,233,023	0.57135	PPAT, PAICS, HOPX, REST, POLR2B, IGFBP7
11	83,875,552	84,970,005	0.63952	TRIB2
11	29,736,720	30,551,963	0.50447	CALM2, EPCAM, MSH2, MSH6, FBXO11, FOXN2
16	75,847,620	76,091,078	0.52570	IRF6, HSD11B1, CAMK1G
19	42,988,287	43,755,425	1.99706	EIF1, JUP, NT5C3B, KLHL10, ACLY, TTC25, CNP, DNAJC7, NKIRAS2, DHX58, KAT2A, HSPB9, RAB5C, STAT5B, STAT5A, STAT3, ATP6V0A1, NAGLU, HSD17B1, COASY, MLX, TUBG1, TUBG2, EZH1, RAMP2, VPS25, CNTD1, PSME3, AOC2, AOC3, SAO, G6PC, AARSD1, RND2, BRCA1, ARL4D, DHX8, ETV4, MEOX1
20	7,103,987	7,736,726	1.50032	GFM2, HEXB, ENC1, UTP15, ANKRA2, CALM
20	65,636,880	67,125,349	0.65687	MTRR, ADCY2, NSUN2, MED10
21	21,333,104	22,991,710	0.67895	ACAN, HAPLN3, MFGE8, RLBP1, FANCI, POLG, TICRR, ANPEP, AP3S2, ZNF710
24	52,165,674	54,752,773	0.53601	POLI, RAB27B, TCF4

BTA: Bos taurus autosomes; bp: base pair.

Table 4. Genomic regions of 10 adjacent SNPs that explain more than 0.5% of the additive genetic variance (Var) for dry mater intake (DMI) in Nelore cattle.

BTA	Start position (bp)	End position (bp)	Var (%)	Genes
2	20,929,001	21,696,086	0.83911	HOXD3, HOXD4, HOXD9, HOXD10, HOXD11, ATF2, CHRNA1
2	120,775,372	122,330,054	0.78975	ECEL1, CHRND, CHRNG, PHC2, RBBP4, ZBTB8A, MARCKSL1, HDAC1, LCK, KHDRBS1, SPOCD1, HCRTR1
5	33,430,648	34,965,958	0.59848	AMIGO2, SCAF11, ARID2
10	6,617,470	7,427,251	0.57428	COL4A3BP, POLK, IQGAP2, F2RL2, F2R
10	3,004,311	3,691,643	0.52988	TRIM36
12	18,440,125	19,212,646	0.65670	MED4, RB1, LPAR6, RCBTB2, CYSLTR2, FNDC3A, MLNR, PHF11, KPNA3
14	21,452,744	21,976,451	0.50976	SPIDR, H3F3C, PRKDC, SNAI2
14	22,297,785	22,983,665	0.56690	NPBWR1, OPRK1
14	24,049,812	24,229,059	0.50996	ATP6V1H, RGS20, TCEA1, SOX17
19	43,001,952	43,948,803	0.96340	JUP, ACLY, CNP, DNAJC7, HCRT, STAT5B, STAT5A, STAT3, ATP6V0A1, NAGLU, HSD17B1, COASY, MLX, TUBG1, TUBG2, EZH1,VPS25, BECN1, PSME3, AOC2, AOC3, SAO, BRCA1, DHX8, ETV4, SOST, DUSP3, PPY, PYY
20	7,103,987	7,736,726	0.85015	HEXB, ANKRA2
21	21,333,104	22,991,710	0.53186	ABHD2, FANCI, RHCG, TICRR, AP3S2, ZNF710, CIB1, VPS33B, PRC1, BLM, CRTC3, ZSCAN2, NMB, AP3B2
21	9,033,285	9,741,507	0.52817	
23	22,300,959	23,477,473	0.56001	CENPQ, RHAG, TFAP2B
29	23,411,243	24,642,061	0.69345	PKHD1, HTATIP2, DBX1, NAV2

BTA: Bos taurus autosomes; bp: base pair.

Table 5. Genomic regions of 10 adjacent SNPs that explain more than 0.5% of the additive genetic variance (Var) for feed efficiency (FE) in Nelore cattle.

BTA	Start position (bp)	End position (bp)	Var (%)	Genes
6	73,547,830	74,233,023	1.18301	PPAT, PAICS, HOPX, REST
7	24,982,024	25,784,499	1.29587	
9	33,173,529	34,265,873	1.05822	NEPN, VGLL2, RFX6
9	12,744,212	13,502,951	0.79536	EEF1A1,
9	34,495,344	35,276,579	0.52239	TSPYL4, FRK
10	6,018,257	7,329,188	0.51571	DRD1
11	84,227,146	84,997,734	1.61074	TRIB2
14	16,387,114	17,752,395	0.77942	TRIB1, ZNF572, RNF139
14	19,649,604	20,725,667	0.63480	
14	18,460,103	19,605,085	0.58282	FBXO32, WDYHV1, ATAD2, ZHX1, DERL1, ZHX2
14	21,224,382	21,735,604	0.55173	H3F3C, PRKDC, UBE2V2, SNAI2
14	15,551,978	16,285,123	0.52712	
16	77,099,277	77,825,967	0.92552	CD34, CD46, ASPM
16	75,847,620	76,091,078	0.84157	IRF6
16	74,134,974	74,161,201	0.59412	NEK2, RCOR3
17	46,858,681	47,425,590	0.83153	PIWIL1
20	7,351,732	8,078,272	0.61095	ANKRA2
20	5,767,456	6,495,026	0.59919	CPEB4, MSX2
24	56,386,139	56,436,773	0.96898	
24	54,964,769	55,980,406	0.74121	TCF4
24	51,961,637	54,724,737	0.53527	POLI

BTA: Bos taurus autosomes; bp: base pair.

Table 6. Genomic regions of 10 adjacent SNPs that explain more than 0.5% of the additive genetic variance (Var) for feed conversion ratio (FCR) in Nelore cattle.

BTA	Start position (bp)	End position (bp)	Var (%)	Genes
3	54,028,274	54,062,811	0.60141	LRRC8D, LRRC8C, GBP6, GBP5
5	87,926,197	88,878,999	0.50680	C2CD5, SPX, IAPP, SLCO1A2, SLCO1B3
7	24,982,024	25,784,499	0.97067	
9	12,744,212	13,502,951	1.20275	EEF1A1
9	33,173,529	34,265,873	0.73280	PLN
9	15,959,442	16,564,251	0.58648	
11	83,875,552	84,970,005	1.01124	TRIB2
14	16,387,114	17,752,395	2.28115	RNF139, DERL1
14	19,649,604	20,725,667	2.26805	
14	21,224,382	21,735,604	2.21004	PRKDC
14	21,967,712	22,317,344	1.80052	SNTG1
14	15,551,978	16,285,123	1.60483	TRIB1
14	18,460,103	19,605,085	1.59205	
14	24,115,422	24,406,302	1.31728	
14	23,510,902	23,929,089	1.25423	OPRK1, SOX17
14	24,437,778	24,590,812	1.09788	
14	24,607,527	24,892,678	1.07645	
14	22,392,760	23,017,421	1.06328	
14	24,909,247	25,307,116	1.02923	PENK
20	5,767,456	6,495,026	0.63336	GFM2
24	56,386,139	56,436,773	0.71319	
24	54,964,769	55,980,406	0.50680	RAB27B

BTA: Bos taurus autosomes; bp: base pair.

Table 7. Genomic regions of 10 adjacent SNPs that explain more than 0.5% of the additive genetic variance (Var) for residual body weight gain (RG) in Nelore cattle.

BTA	Start position (bp)	End position (bp)	Var (%)	Genes
7	24,982,024	25,784,499	0.73172	
9	12,744,212	13,502,951	0.64508	EEF1A1, CD109
9	15,953,490	16,452,859	0.62922	
11	84,227,146	84,997,734	1.65889	TRIB2
14	16,387,114	17,752,395	1.74571	NSMCE2, ZNF572, MTSS1, RNF139
14	21,224,382	21,735,604	1.39310	SPIDR, H3F3C, PRKDC, UBE2V2, SNAI2
14	18,460,103	19,605,085	1.38702	FBXO32, WDYHV1, ATAD2, ZHX1, DERL1, ZHX2
14	19,649,604	20,725,667	1.37614	HAS2
14	22,297,785	22,983,665	1.31933	ST18
14	21,778,139	22,251,785	1.16037	
14	15,551,978	16,285,123	0.95066	TRIB1
14	24,008,839	24,225,369	0.83847	
14	23,510,902	23,929,089	0.82056	RB1CC1, OPRK1, RGS20, TCEA1, POLR2K, SOX17
14	24,237,304	24,553,162	0.75930	
14	25,528,516	26,385,476	0.70828	UBXN2B
14	2,194,228	2,342,883	0.68498	VPS28, CPSF1, SCRT1, HSF1, BOP1, SCX, MAF1, SHARPIN, CYC1, PUF60, TIGD5, EEF1D, NAPRT, MAFA, SLURP1
14	24,909,247	25,307,116	0.68013	TGS1, LYN, PLAG1, PENK
14	24,582,124	24,828,922	0.62384	
16	47,341,761	49,343,163	0.51830	PHF13, NOL9, ESPN, HES2, CHD5, NPHP4, CSRP1
17	70,443,042	71,146,543	0.60670	CHEK2, HSCB, XBP1, ZNRF3, RHBDD3, NF2, HORMAD2, LIF, OSM, SEC14L2
18	17,497,121	18,822,874	1.11781	C18H16orf78, ZNF423, BRD7, NKD1, SNX20, NOD2, CYLD
18	16,307,788	17,399,669	1.09141	LONP2, SIAH1, N4BP1
24	56,386,139	56,436,773	0.84133	
24	54,964,769	55,980,406	0.76039	TCF4
24	51,961,637	54,724,737	0.63574	POLI, C24H18orf54
29	13,219,091	14,408,041	0.79633	

BTA: Bos taurus autosomes; bp: base pair.

Table 8. Genomic regions of 10 adjacent SNPs that explain more than 0.5% of the additive genetic variance (Var) for residual intake and body weight gain (RIG) in Nelore cattle.

BTA	Start position (bp)	End position (bp)	Var (%)	Genes
1	95,979,250	96,791,940	0.71167	ECT2, TNIK, SLC2A2
1	129,646,287	130,413,011	0.50496	KPNA6
2	20,929,001	21,696,086	1.02488	ATF2, CHRNA1
2	120,775,372	122,330,054	0.85774	PDE6D, ECEL1, CHRND, CHRNG, PHC2, AK2, RBBP4, ZBTB8A, HDAC1, LCK, KHDRBS1, SPOCD1, HCRTR1, TINAGL1
2	19,851,161	20,896,601	0.59712	NFE2L2, HNRNPA3, HOXD3, HOXD4, HOXD9, HOXD10, HOXD11
5	99,077,991	100,222,618	0.69229	TAS2R42, TAS2R46, T2R65A, T2R12, BOTA-T2R10B, TAS2R10, T2R10C, YBX3, STYK1, KLRJ1, KLRD1, GABARAPL1, OLR1, CLEC7A, CLEC1A, CLEC1B, CLEC12B
5	33,732,100	34,992,983	0.57163	SCAF11, ARID2
6	73,547,830	74,233,023	0.61928	PPAT, PAICS, HOPX, REST, POLR2B, IGFBP7
9	33,173,529	34,265,873	1.02901	ROS1, KPNA5, RSPH4A
11	29,736,720	30,551,963	0.51941	MSH2, MSH6, LHCGR
14	19,649,604	20,725,667	1.72493	
14	21,224,382	21,735,604	1.43592	HAS2, SPIDR, H3F3C, PRKDC, UBE2V2, SNAI2
14	21,976,451	22,392,760	1.37106	
14	16,387,114	17,752,395	1.09489	ZNF572, MTSS1, TATDN1, RNF139, ANXA13
14	24,543,370	24,643,266	0.93121	
14	24,864,286	25,147,967	0.89330	LYN
14	15,551,978	16,285,123	0.88898	
14	23,929,089	24,222,338	0.87523	POLR2K, SOX17
14	18,460,103	19,605,085	0.87461	FBXO32, ATAD2, ZHX1, DERL1, ZHX2
14	24,225,369	24,539,053	0.80941	
14	23,252,097	23,893,220	0.69756	RB1CC1, NPBWR1, OPRK1, TCEA1
19	5,974,265	6,709,868	0.69818	

BTA: Bos taurus autosomes; bp: base pair.

Table 8. Genomic regions of 10 adjacent SNPs that explain more than 0.5% of the additive genetic variance (Var) for residual intake and body weight gain (RIG) in Nelore cattle (Continued).

BTA	Start position (bp)	End position (bp)	Var (%)	Genes
19	42,988,287	43,755,425	0.53954	NT5C3B, ACLY, CNP, DNAJC7, HCRT, STAT5B, STAT5A, STAT3, ATP6V0A1, HSD17B1, COASY, TUBG1, TUBG2, EZH1, VPS25, BECN1, PSME3, AOC2, AOC3, SAO, BRCA1, DHX8
20	7,077,978	7,661,649	0.93475	
20	66,782,391	67,959,003	0.72484	MED10
21	21,333,104	22,991,710	0.64695	ACAN, HAPLN3, MFGE8, FANCI, TICRR, AP3S2, CIB1, VPS33B, PRC1, HDDC3, MAN2A2, FES, BLM, CRTC3, ZSCAN2, NMB, PDE8A, AP3B2
30	86,838,544	87,524,773	0.58080	

BTA: Bos taurus autosomes; bp: base pair.

Table 9. KEGG pathways and Gene Ontology terms revealed by DAVID analyses for feed efficiency related traits in Nelore cattle.

Term	N	P-value	Genes	FDR
Biological process				
GO:0007218~neuropeptide signaling pathway	10	0.00076	*HCRTR1, HCRT, PPY, PENK, ECEL1, CYSLTR2, OPRK1, NPBWR1, NMB, PYY*	1.27
GO:0071498~cellular response to fluid shear stress	4	0.00313	*MTSS1, XBP1, HAS2, NFE2L2*	5.16
GO:0008285~negative regulation of cell proliferation	17	0.00444	*NF2, BECN1, REST, RB1, STAT3, OSM, LIF, MSX2, HSF1, IRF6, BRD7, TFAP2B, RNF139, DIS3L2, C24H18ORF54, CIB1, F2R*	7.23
GO:0048863~stem cell differentiation	5	0.00797	*EPCAM, LIF, MSX2, HOXD4, ETV4*	12.64
GO:0071479~cellular response to ionizing radiation	5	0.01077	*BLM, SPIDR, SNAI2, EEF1D, ECT2*	16.71
GO:0038083~peptidyl-tyrosine autophosphorylation	6	0.01149	*FRK, STYK1, LYN, LCK, FES, ROS1*	17.73
GO:0009308~amine metabolic process	3	0.01159	*SAO, AOC2, AOC3*	17.87
GO:0035137~hindlimb morphogenesis	3	0.01159	*HOXD9, TFAP2B, HOXD10*	17.87
GO:0090090~negative regulation of canonical Wnt signaling pathway	9	0.01162	*CYLD, NPHP4, RGS20, NKD1, SOST, HDAC1, SOX17, SNAI2, ZNRF3*	17.92
GO:0006357~regulation of transcription from RNA polymerase II promoter	17	0.01303	*ANKRA2, RFX4, RFX6, RB1, STAT3, ATF2, MED4, MLX, BRD7, HOPX, ZNF710, TCEA1, NFE2L2, MAFA, ASCL4, DBX1, ETV4*	19.87
GO:0043123~positive regulation of I-kappaB kinase/NF-kappaB signaling	11	0.01447	*TNFSF10, NOD2, GOLT1B, SHARPIN, PLEKHG5, TRIM13, EEF1D, ECT2, TRIM62, TRAF5, F2R*	21.82
GO:0031648~protein destabilization	5	0.02032	*DERL1, XBP1, RNF139, PRKDC, SOX17*	29.30
GO:0070493~thrombin receptor signaling pathway	3	0.02321	*F2RL2, IQGAP2, F2R*	32.75
GO:2001214~positive regulation of vasculogenesis	3	0.02321	*RAMP2, CD34, TMEM100*	32.75
GO:0019233~sensory perception of pain	5	0.02523	*PENK, IAPP, OPRK1, NIPSNAP1, HOXD1*	35.06
GO:0045647~negative regulation of erythrocyte differentiation	3	0.03024	*STAT5A, STAT5B, GAS2L1*	40.46
GO:0001580~detection of chemical stimulus involved in sensory perception of bitter taste	4	0.03626	*T2R10C, T2R12, BOTA-T2R10B, TAS2R10*	46.41

N: number of genes; P-values: significance level at 5%; FDR: False Discovery Rate

Table 9. KEGG pathways and Gene Ontology terms revealed by DAVID analyses for feed efficiency related traits in Nelore cattle (Continued).

Term	N	P-value	Genes	FDR
Biological process				
GO:0006351~transcription, DNA-templated	31	0.03694	*EZH1, HINT1, STAT5A, STAT5B, REST, MAF1, SEC14L2, MSX2, HSF1, XBP1, TCEA1, SCX, RBBP4, PHF11, SNAI2, SPOCD1, ZSCAN2, BRCA1, MED10, STAT3, HOXD9, HDAC1, IRF6, HOXD3, HES2, HOPX, NFE2L2, PUF60, ZNF572, ZBTB8A, VPS25*	47.05
GO:0008284~positive regulation of cell proliferation	16	0.03942	*PRC1, MARCKSL1, PKHD1, STAT5A, STAT5B, ST8SIA1, OSM, EPCAM, LIF, HDAC1, TFAP2B, SDCBP, HAS2, SCX, CIB1, F2R*	49.30
GO:0042149~cellular response to glucose starvation	4	0.04585	*MTMR3, XBP1, BECN1, NFE2L2*	54.74
GO:0051930~regulation of sensory perception of pain	3	0.04639	*SPX, TMEM100, F2R*	55.17
Molecular function				
GO:0030246~carbohydrate binding	10	0.00489	*CLEC1A, MAN2A2, OLR1, CD34, KLRJ1, CLEC12B, ACAN, CLEC7A, KLRD1, CLEC1B*	6.83
GO:0033038~bitter taste receptor activity	4	0.00743	*T2R10C, T2R12, BOTA-T2R10B, TAS2R10*	10.20
GO:0008131~primary amine oxidase activity	3	0.01143	*SAO, AOC2, AOC3*	15.28
GO:0003824~catalytic activity	8	0.01697	*PHKB, HINT1, SYN3, CDADC1, ISOC1, AZIN2, PGGT1B, AASDH*	21.87
GO:0008565~protein transporter activity	7	0.01820	*RAMP2, AP1B1, AP3S2, KPNA6, KPNA5, IPO9, KPNA3*	23.27
GO:0005184~neuropeptide hormone activity	4	0.04018	*PPY, PENK, SPX, PYY*	44.66
Cellular component				
GO:0000228~nuclear chromosome	4	0.00981	*MSH6, MSH2, SPIDR, THOC5*	12.66
GO:0031234~extrinsic component of cytoplasmic side of plasma membrane	7	0.01306	*FRK, CYLD, STYK1, KCNAB2, LYN, LCK, FES*	16.52
GO:0005654~nucleoplasm	62	0.01768	*HTATIP2, ZMAT5, PRC1, TIMM17A, STAT5A, CNP, MAF1, HOXD11, SENP6, ACOT7, HSF1, FANCI, RSPH4A, COL4A3BP, DNAJC7, PHC2, CIB1, KHDRBS1, POLK, TNIK, ZHX1, ZHX2, PARP10, TATDN1, MTRR, RECQL,*	

N: number of genes; P-values: significance level at 5%; FDR: False Discovery Rate

Table 9. KEGG pathways and Gene Ontology terms revealed by DAVID analyses for feed efficiency related traits in Nelore cattle (Continued).

Term	N	P-value	Genes	FDR
Cellular component				
GO:0005654~nucleoplasm	62	0.01768	*NAV2, HOXD3, KPNA6, KPNA5, PSME3, KPNA3, CRTC3, COASY, HSD17B1, TICRR, GSDMD, PRKDC, BOP1, ARID2, SCRIB, ATF2, HNRNPA3,MTMR3, SCAF11, ETNK1, SPIDR, DHX8, MSH6, ZBTB48, OLR1, CENPQ, ATAD2, ACLY, SF3A1, STAT3, DUSP3, ATP6V0A1, ANXA13, FBXO32, CLEC7A, PUF60*	21.72
GO:0009986~cell surface	20	0.02864	*RAMP2, CLSTN2, CD109, IQGAP2, LY6K, FURIN, EPCAM, NOD2, LYNX1, LY6D, CD46, CCR10, CLEC9A, KCNN2, CHRNA1, GHSR, ANO6, ROS1, AOC3, F2R*	32.89
GO:0030123~AP-3 adaptor complex	3	0.04704	*AP3B2, AP3S2, VPS33B*	48.39
KEGG pathway				
bta04742:Taste transduction	7	0.00098	*T2R10C, TAS2R46, TAS2R42, T2R12, TAS1R1, BOTA-T2R10B, TAS2R10*	1.25
bta04976:Bile secretion	8	0.00413	*SLCO1B3, NCEH1, ADCY2, SLCO1A2, ADCY7, HMGCR, CYP7A1, KCNN2*	5.15
bta04922:Glucagon signaling pathway	9	0.00759	*LDHB, G6PC, ADCY2, CALM, PHKB, SLC2A2, GYS2, CALM2, ATF2*	9.27
bta00230:Purine metabolism	12	0.01689	*PDE6D, ADCY2, ADCY7, NT5C3B, POLR2K, AK2, HDDC3, PDE8A, PAICS, POLR3B, PPAT, POLR2B*	19.55
bta04950:Maturity onset diabetes of the young	4	0.04192	*IAPP, RFX6, SLC2A2, MAFA*	42.14

N: number of genes; P-values: significance level at 5%; FDR: False Discovery Rate

List of Figures Legends

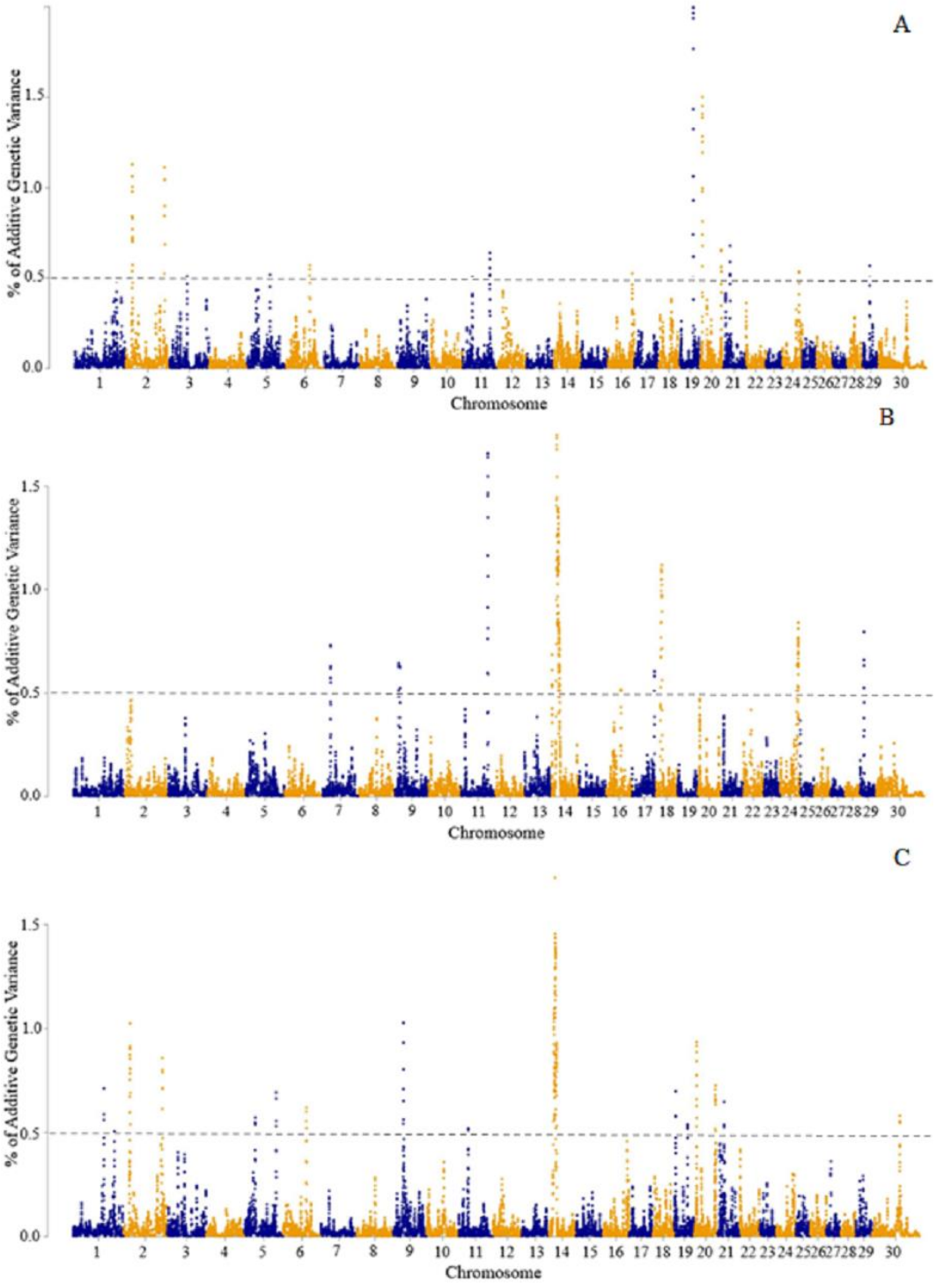

Figure 1. Proportion of additive genetic variance explained by windows of 10 adjacent SNPs for residual feed intake (RFI - A), residual body weight gain (RG – B) and residual intake and body weight gain (RIG – C) in Nelore cattle.

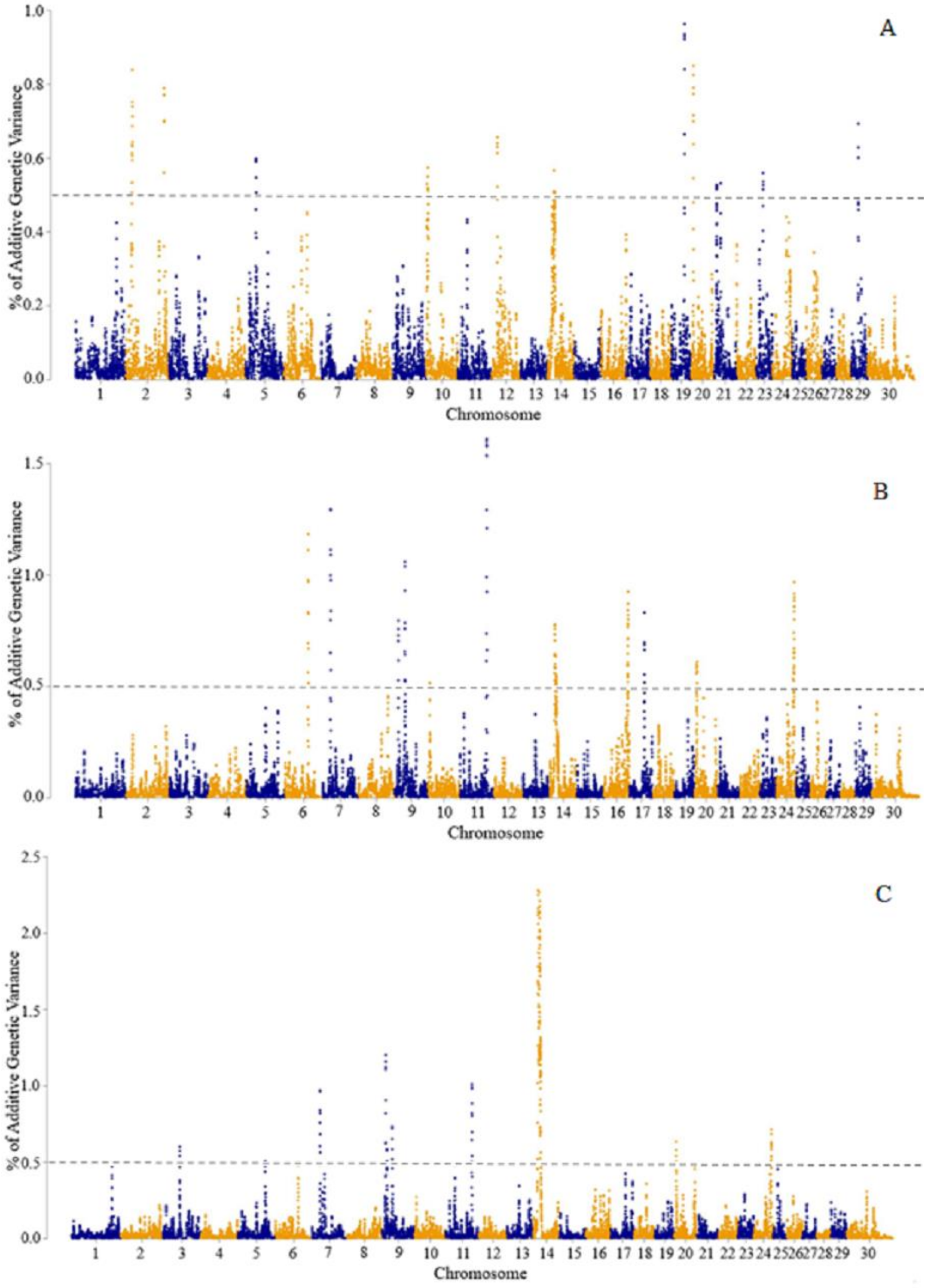

Figure 2. Proportion of additive genetic variance explained by windows of 10 adjacent SNPs for dry matter intake (DMI - A), feed efficiency (FE – B) and feed conversion ratio (FCR – C) in Nelore cattle.

APPENDIX 1

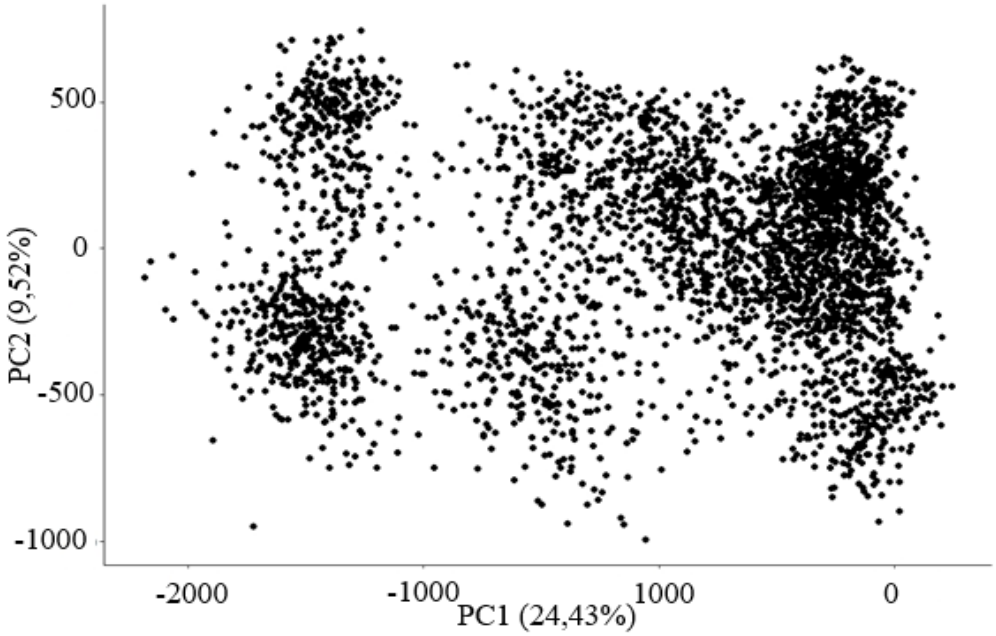

FIGURE A1 Principal component analyses of genomic relationship among Nelore cattle evaluated for related feed efficiency traits.

CAPÍTULO 5 – CONSIDERAÇÕES FINAIS

A base de dados utilizada neste estudo foi composta por informações provenientes de vários rebanhos, localizados em todas as regiões do país e com animais submetidos a diferentes condições de criação. Isso proporcionou uma maior abrangência dos resultados obtidos, à nível populacional. Dados desse tipo de fenótipo são raros em animais *Bos indicus*, uma vez que a maioria dos estudos genéticos e genômicos avaliando eficiência alimentar em raças zebuínas têm sido realizados com populações experimentais e de pequeno tamanho amostral. Além disso, poucos estudos com bovinos de corte têm quantificado as relações genéticas entre eficiência alimentar e outras características de importância econômica, bem como a resposta da seleção para eficiência alimentar, o que justifica a realização do presente estudo.

As medidas de eficiência alimentar, tais como consumo alimentar residual (CAR), consumo de matéria seca (CMS), eficiência alimentar (EA), conversão alimentar (CA), ganho em peso residual (GPR) e consumo e ganho residual (CGR) tiveram seus parâmetros genéticos estimados nesse estudo, apresentando variabilidade genética e herdabilidade moderada para CAR, CMS, GPR e CGR. A seleção para melhoria da eficiência alimentar, baseada em CAR, GPR e CGR pode não afetar o crescimento, reprodução e carcaça, assim é possível aumentar a eficiência alimentar sem afetar a desempenho de bovinos Nelore. Além disso, maior ganho genético na maximização da eficiência alimentar pode ser obtido com a utilização dessas características como critério de seleção, em comparação a CA e EA.

Apesar do moderado sinergismo entre as características de eficiência alimentar, estas apresentam diferentes *backgrounds* genéticos e podem levar a diferentes respostas na melhoria do uso de alimento. Considerando os diferentes sistemas de produção de bovinos, a escolha do critério de seleção para eficiência alimentar mais adequado vai depender do sistema e do objetivo de produção. Enquanto o CAR pode ser um critério de seleção efetivo para redução do consumo e indicado para ser utilizado em sistemas de produção com baixa oferta de alimento, o CGR permite a seleção de animais de baixo consumo e maior ganho em peso residual e é indicado para sistemas mais intensivos de produção. Recomenda-se a seleção direta para CAR, GPR e CGR visando melhoria da eficiência alimentar. Com isso, é necessária a mensuração dos fenótipos para eficiência alimentar em bovinos Nelore. O CAR, GPR e CGR podem ser incluídas como critérios de seleção adicional em índices de seleção, associadas a medidas de crescimento, reprodução e carcaça, para obtenção de animais com maior

aproveitamento do alimento consumido. Por outro lado, a inclusão de CA ou EA como critério de seleção pode trazer prejuízos as características de crescimento e carcaça.

Os métodos bayesianos e ssGBLUP se mostraram opções adequadas para a obtenção de valores genômicos para eficiência alimentar em bovinos Nelore, com similaridade quanto à habilidade e o viés de predição. Esses resultados são esperados para características de natureza poligênica, grandes populações experimentais, conectadas pelo pedigree e com a maior proporção de animais com informações fenotípicas e genotípicas. Assim, outros fatores devem ser avaliados para identificação do método de predição utilizado, como a facilidade de implementação, demanda computacional, disponibilidade dos dados, tamanho populacional, entre outros. As estimativas de herdabilidade apresentam grande influência sobre a habilidade de predição genômica, de forma que características de baixa herdabilidade, como EA e CAR, apresentam também baixa acurácia.

Métodos de validação cruzada aleatórios podem ser mais vantajosos para avaliação de características de eficiência alimentar em bovinos Nelore, pois são populações jovens e com poucas gerações registradas. Além disso, diferenças no grau de parentesco genômico e no tamanho dos grupos de validação influenciam a habilidade de predição dos esquemas de validação. Ainda assim, para características de maior herdabilidade pode ser viável a validação por idade ou acurácia do EBV, sendo uma alternativa prática de avaliação, pois permitirá a predição do valor genômico de animais jovens de forma acurada, além de prever o desempenho das gerações futuras e antecipar a tomada de decisões.

Os pseudo-fenótipos passam por pré-processamentos, o que leva a diferentes sinais genéticos e assim diferentes efeitos nas análises de predição genômica. Além disso, a acurácia de pseudo-fenótipos como o valor genético estimado (EBV) e EBV desregredido (DEBV) é dependente da herdabilidade da característica. Assim, para características de baixa herdabilidade, o fenótipo e o fenótipo ajustado para os efeitos fixos (Y*) se mostrou mais adequado para as estimativas dos efeitos dos marcadores e dos valores genômicos utilizando ssGBLUP e métodos bayesianos, respectivamente.

É importante enfatizar que foram utilizados painéis de baixa densidade neste estudo, o que permite inferir que mesmo nestes cenários, os métodos de predição podem fornecer estimativas confiáveis dos valores genômicos para características de eficiência alimentar, principalmente, para CAR, CMS, GPR e CGR. Essa estratégia possui uma ótima aplicação prática, uma vez que a genotipagem com painéis de baixa densidade resulta em custos mais baixos e maior possibilidade de adoção pelos criadores.

Foi realizado análise de GWAS em passo único ponderado e estudo de enriquecimento de vias metabólicas para eficiência alimentar em bovinos Nelore, no qual um grande número de regiões genômicas foram identificadas com possível influencia no CAR, CMS, EA, CA, GPR e CGR, respectivamente. Destas, foram observadas regiões que explicaram mais de 0,5% da variação genética aditiva para mais de uma característica avaliada, confirmando efeitos pleiotrópicos atuando na expressão de características relacionadas à eficiência alimentar. Os efeitos pleiotrópicos justificam a moderada correlação genética obtida entre as características relacionadas à eficiência alimentar.

Processos envolvidos, principalmente, no metabolismo da insulina, leptina, glicose, proteínas e lipídios, balanço energético, estresse oxidativo, transporte de íons, sistema *zinc fingers*, secreção biliar, saciedade, comportamento alimentar, salivação, digestão e absorção de nutrientes parecem regular as características relacionadas à eficiência alimentar em bovinos Nelore. De maneira geral, foi observado que a eficiência alimentar de bovinos Nelore está relacionada a processos associados à produção e gasto de energia. Uma das limitações a seleção para eficiência alimentar é a influencia na composição corporal. Contudo, os resultados obtidos nesse estudo demonstram que o gasto energético e a exigência de mantença podem ser importantes vias para estudos adicionais e como estratégia de seleção de animais de maior eficiência alimentar, sem afetar a composição de carcaça e assim corrigir possíveis influencias negativas da utilização dessas características como critério de seleção.

Algumas das regiões genômicas e genes identificados neste estudo não foram relatados anteriormente em bancos de dados públicos relacionados à eficiência alimentar para bovinos. Assim, acredita-se que estas características em bovinos Nelore sejam reguladas por diferentes mecanismos biológicos que outras raças bovinas ou espécies; e vários mecanismos fisiológicos podem estar relacionadas ao controle da eficiência alimentar em bovinos Nelore.

As informações de parâmetros genéticos obtidas para características relacionadas à eficiência alimentar e sua relação com outras características de importância econômica possibilitam sua ampla inclusão nos programas de melhoramento genético e a identificação de animais mais eficientes para a raça Nelore, sem implicações negativas para outras características, como carcaça e reprodução.

A utilização de predições genômicas aliadas a avaliação genética possibilita a estimação dos valores genômicos dos animais de forma acurada, mesmo aqueles jovens ou que ainda não apresentaram fenótipo. Essas informações podem acelerar o ganho genético e

também auxiliar a inclusão de características relacionadas à eficiência alimentar de forma maciça em programas de melhoramento genético de bovinos Nelore.

Os genes e regiões genômicas identificados neste estudo permitem uma melhor compreensão dos mecanismos biológicos e genéticos que resultam na expressão fenotípica de características relacionadas à eficiência alimentar em bovinos Nelore. Essas informações auxiliam no entendimento de como se processa a base genética e biológica de características relacionadas à eficiência alimentar, podendo contribuir para a inclusão das mesmas no processo de seleção e servindo de base para a realização de estudos de genômica funcional.

ANEXO A - Parecer de aprovação do Projeto pelo Comitê de Ética da UFG - CEUA

MINISTÉRIO DA EDUCAÇÃO
UNIVERSIDADE FEDERAL DE GOIÁS
PRÓ-REITORIA DE PESQUISA E INOVAÇÃO
COMISSÃO DE ÉTICA NO USO DE ANIMAIS/CEUA

Goiânia, 17 de dezembro de 2018.

PARECER CONSUBSTANCIADO REFERENTE AO PROJETO DE PESQUISA DO PROTOCOLO N. 088/18

I - Finalidade do projeto de pesquisa: Pesquisa - Doutorado

- **Data de apresentação a CEUA:** 23/10/2018
- **Título do projeto:** Associação e seleção genômica para eficiência alimentar em bovinos Nelore avaliados no estado de Goiás/GO
- **Pesquisador Coordenador no SIGAA/ Unidade:** Cláudio Ulhôa Magnabosco/EVZ-UFG
- **Pesquisador Responsável/ Unidade:** Ludmilla Costa Brunes/EVZ-UFG
- **Pesquisadores Participantes/ Unidade:** Eduardo da Costa Eifert/Embrapa Cerrados, Adriano Santana Crozara/Embrapa Arroz e Feijão
- **Médico Veterinário/CRMV:** Marcos Fernando Oliveira e Costa/ 3037-GO
- **Unidade onde será realizada a pesquisa:** Centro de desempenho animal, Embrapa Arroz e Feijão, Zona Rural, Santo Antônio do Goiás/GO

III- Objetivos e justificativa do projeto: Estimar a variabilidade genética e parâmetros genéticos para características de eficiência alimentar e suas associações genéticas com características de produção, reprodução e carcaça em bovinos da raça Nelore, além de realizar estudos associação e seleção genômica ampla do consumo alimentar residual em bovinos da raça Nelore, visando trazer subsídios para incorporação do CAR e da informação genômica nas avaliações genéticas de bovinos de corte no Brasil. **Justificativa:** Considerando a difícil e onerosa mensuração de características como o CAR, o desenvolvimento de estudos com marcadores moleculares e informações genômicas para as características relacionadas à eficiência alimentar apresenta grande importância para os programas de melhoramento genético.

IV - Sumário do projeto:

- **Discussão sobre a possibilidade de métodos alternativos e necessidade do número de animais:** Os pesquisadores relatam que não há possibilidade de métodos alternativos.
- **PREVÊ PROJETO PILOTO:** NÂO
- **Descrição do animal utilizado (Explicitar: espécie/ linhagem/ sexo (informar número por sexo)/ peso e/ou idade etc):** Bovinos machos, nelore, de 24 a 27 meses de idade pesando 420Kg.
- **ESPÉCIE ANIMAL UTILIZADA/ NÚMERO TOTAL DE ANIMAIS/ NÚMERO DE ANIMAIS POR TRATAMENTO OU GRUPOEXPERIMENTAL:** 300 BOVINOS NELORE.
- **Fonte de obtenção do animal:** Centro de desempenho animal, Embrapa Arroz e Feijão.

- **Descrição das instalações utilizadas e número de animais/área/qualidade do ambiente (ar, temperatura, umidade), alimentação/hidratação**: Haverá água limpa *ad libitum* aos animais, com lavagem de bebedouros a cada 02 dias, tanto nas avaliações a pasto quanto confinada. A pasto, os animais terão acesso à vontade a pastagem de *Brachiaria decumbens* cv. Marandu, em sistema de rotação de piquetes, com fornecimento de sal mineral ou suplementação uma vez ao dia. Temperatura média anual de 23ºC, confinamento de 12m^2/animal, 50 animais/baia, terra batida, com sombrites.
- **Utilização de agente infeccioso/gravidade da infecção a ser observada e análise dos riscos aos pesquisadores/alunos:** Não se aplica.
- **Procedimentos experimentais do projeto de pesquisa:** Recepção dos animais oriundos das fazendas parceiras, no Centro de Desempenho Animal em Santo Antônio de Goiás, geralmente, nos meses de maio. Todos os animais permanecerão a pasto, em gramínea *Brachiaria Decumbens* cv. Marandu, em sistema de pastejo rotacionado, por 294 dias, sendo 70 dias o período de adaptação. Neste período, os animais serão pesados e submetidos a mensuração do perímetro escrotal a cada 56 dias, precedido de jejum de sólidos de 14 horas. Ao final deste período, será realizada avaliação de ultrassom de carcaça e visual. Todos os animais permanecerão à pasto, em gramínea *Brachiaria Decumbens* cv. marandu até que as instalações do confinamento e do curral estejam em funcionamento e devidamente adequadas. Após e com o curral devidamente instalado (geralmente, no mês de junho), os animais serão conduzidos ao curral e contidos no brete para brincagem. Manejo o qual será inserido em uma das orelhas a *tag* que permite a identificação do animal quando acessar o cocho ou a balança corporal. Após inserido, será cuidado o local com iodo 90% e mata-bicheira, para evitar quaisquer contaminações. Identificados, os animais seguirão para oconfinamento, onde passarão 20 dias por um período de adaptação, tanto das instalações, quanto da dieta. Todos os animais terão acesso a água e ração *ad libitum*. A dieta será fornecida duas vezes ao dia, as 08:00e as 15:30. Passados os 20 primeiros dias, os animais ficarão em jejum de sólidos por 14 horas, para que sejam conduzidos até o curral, contidos no brete e pesados na balança tradicional. Após a pesagem os animais retornarão ao confinamento, onde terão novamente acesso a ração. O jejum de sólidos volta a ser realizado a cada 14 dias, para nova pesagem e em seguida retornarem ao confinamento. No último dia de experimentação, ou seja, ao final dos 90 dias, os animais passarão por uma avaliação de carcaça através daultrassonografia, obtendo imagens do músculo *Longissimus dorsi* na região entre 12ª e 13ª costelas e sobreo músculo *Biceps femoris* (garupa). As imagens serão gravadas em computador portátil e analisadas por técnico. As características medidas pela ultrassonografia serão: espessura de gordura subcutânea sobre a região entre as 12ª e 13ª costela (EGS, mm), espessura de gordura subcutânea sobre a garupa (EGP, mm) eárea de olho de lombo (cm²). Após o período de experimentação e coleta dos dados os animais retornarão ao pasto, aguardando que os proprietários dos animais os busquem para retorno às origens.
- **Grau de invasividade:** Grau 1
- **Material foi obtido ou será utilizado em outros projetos (informar protocolo CEUA quando houver):** Sim, projeto n° 123/17, título: Obtenção de consumo e peso vivo utilizando equipamentos eletrônicos e sua aplicação em função da eficiência alimentar.

- **Métodos utilizados para minimizar o sofrimento e aumentar o bem-estar dos animais antes, durante e após a pesquisa (Pontos Finais Humanitários):** Todo o curral é construído visando o bemestar animal, o manejo será feito de maneira racional, não utilizando choques, objetos pontiagudos ou agressão ao animal. O animal terá fácil acesso ao cocho e ao bebedouro, além de espaço suficiente de sombreamento. Será utilizado o seguinte preceito: quanto menor a influência humana, mais precisa será a resposta a pesquisa
- **Método de eutanásia:** Não se aplica, pois, os animais retornarão às suas fazendas de origem.
- **Destino do animal:** Retorno à fazenda de origem.

- **V – Comentários do relator frente às orientações da CEUA:**
- **Quanto aos documentos exigidos pela CEUA/UFG:** Completo (Ficha de protocolo, certidão de ata, termo de responsabilidade, termo de autorização local – Embrapa, TCLE, projeto de pesquisa e CD com todos os documentos).
- **Quanto aos cuidados e manejo dos animais e riscos aos pesquisadores:** Todos os EPIs necessários serão fornecidos aos envolvidos no trabalho. Há o risco de ser surpreendido por alguma reação do animal, como coice ou cabeçada, durante o manejo no curral, no entanto todo o trabalho será feito com cuidado e de forma racional, no intuito de manter os animais os mais tranquilos possíveis.

VI - PARECER DA CEUA:

De acordo com a documentação apresentada à CEUA, o projeto foi considerado **APROVADO** pela *Comissão de Ética no Uso de Animais/CEUA* da Universidade Federal de Goiás.

Reiteramos a importância deste Parecer Consubstanciado, e lembramos que o(a) pesquisador(a) responsável deverá encaminhar à CEUA-PRPI-UFG o Relatório Final baseado na conclusão do estudo e na incidência de publicações decorrentes deste, de acordo com o disposto na Lei nº. 11.794 de 08/10/2008, e Resolução Normativa nº. 01, de 09/07/2010 do Conselho Nacional de Controle de Experimentação Animal-CONCEA. O prazo para entrega do Relatório é de até 30 dias após o encerramento da pesquisa, prevista para conclusão em 31/12/2021.

MINISTÉRIO DA EDUCAÇÃO
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PRÓ-REITORIA DE PESQUISA E INOVAÇÃO
COMISSÃO DE ÉTICA NO USO DE ANIMAIS/CEUA

C E RT I F I C A D O

Certificamos que a proposta intitulada "**Associação e seleção genômica para eficiência alimentar em bovinos Nelore avaliados no estado de Goiás**", registrada com o protocolo **nº 088/18**, sob a responsabilidade de **Cláudio Ulhôa Magnabosco** e **Ludmilla Costa Brunes,** que envolve a produção, manutenção ou utilização de animais pertencentes ao filo Chordata, subfilo Vertebrata (exceto humanos), para fins de pesquisacientífica - encontra-se de acordo com os preceitos da Lei nº 11.794, de 8 de outubro de 2008, do Decreto nº 6.899, de 15 de julho de 2009, e com as normas editadas pelo Conselho Nacional de Controle de Experimentação Animal (CONCEA), e foi aprovada pela COMISSÃO DE ÉTICA NO USO DE ANIMAIS (CEUA) da Universidade Federal de Goiás (UFG), em reunião de **17/12/2018**.

- Finalidade: ( ) Ensino (X) Pesquisa Científica
- Vigência da autorização, início: 17/12/2018 e fim: 31/12/2021
- Espécie/linhagem/raça: Bovino/Nelore
- Nº de animais autorizados: 300
- Peso/Idade: 420Kg, 24-27meses
- Sexo: machos
- Origem (fornecedor): Centro de Desempenho animal, Embrapa Arroz e Feijão.

Coordenadora da CEUA/PRPI/UFG