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Candidate genes for carcass traits in a tropical-adapted Brazilian composite beef breed

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ABSTRACT. Backfat thickness (BFT) and ribeye area (REA) are important production traits but, because they are measured late in the animal's life, they have not been efficiently included in breeding programs. The aim of this study was to evaluate whether single nucleotide polymorphisms (SNPs) mapped to the leptin, *PPARGC1A*, *PSMC1*, *CRH*, and *FABP4* genes, which influence BFT and REA in Canchim cattle, a composite beef breed (5/8 Charolais + 3/8 Zebu). BFT and REA phenotypic records were obtained by ultrasound measurements from 18-month-old animals. All SNP markers were genotyped by restriction fragment length polymorphism-polymerase chain reaction. Restricted maximum likelihood analysis revealed that the non-synonymous SNP located in exon 2 of the *FABP4* gene has an additive effect on BFT ($P \leq 0.05$). Significant allele substitution

effects showed that the substitution of G by A may lead to a decrease of 0.1055 mm in mean BFT. This information can be used for inclusion of this trait-associated marker in commercial SNP panels.

Key words: Backfat thickness; Ribeye area; Canchim cattle ; Single nucleotide polymorphism

INTRODUCTION

The commercial value of bovine carcasses is influenced by several factors, such as weight and meat quality traits. An optimum carcass must contain maximum muscle, minimum bone, an adequate amount of fat, and good palatability. The Canchim is a composite Brazilian breed, of 5/8 Charolais and 3/8 Zebu, produced to combine fitness traits for tropical climates of the Zebu, with the higher reproduction efficiency and beef quality of the Charolais. Currently there are two genetic groups in the Canchim breed: MA (offspring of Charolais bulls and 1/2 Canchim + 1/2 Zebu cows) and CA (offspring of MA x MA, MA x Canchim or Canchim x Canchim). The Canchim breed has shown good growth potential and tropical adaptation, but suboptimal fat deposition.

Quantitative trait loci (QTL) for backfat thickness (BFT) (Moore et al*.,* 2003), ribeye area (REA) (Mizoguchi et al., 2006), and weight at different ages (Takasuga et al., 2007) have been mapped to bovine chromosomes 4, 6, 10, and 14 (BTA4, 6, 10, and 14). The identification of candidate genes that underlie QTL in production traits would enhance knowledge of the biology of phenotypic profiles and genetic variance of traits. Generally, candidate genes are selected based on their physiological or biochemical function and position. Some genes mapped to these chromosomes, such as leptin; peroxisome proliferative active receptor gamma coactivator 1A (*PPARGC1A*); proteasome 26S subunit ATPase 1 (*PSMC1*); corticotropin releasing hormone (*CRH*); and fatty acid binding protein 4 (*FABP4*), have been suggested as candidates that may influence production traits (Buchanan et al., 2002; Liefers et al., 2003; Kononoff et al., 2005; Wibowo et al., 2007; Cho et al., 2008; Guo et al., 2008a; Soria et al., 2009).

Considering these findings, leptin, *PPARGC1A*, *PSMC1*, *CRH*, and *FABP4* were selected as candidates related to production traits. In order to test this hypothesis, association studies were performed to evaluate whether single nucleotide polymorphisms (SNPs) located on these genes are associated with BFT and REA in a population of Canchim cattle raised exclusively on pasture.

MATERIAL AND METHODS

Animals and phenotypic data

Data were collected by *in vivo* ultrasound from 648 Canchim cattle from CA and MA genetic groups, including bulls and heifers. They were raised on pasture in seven Brazilian herds. The animals were born between 2003 and 2005 and were of known pedigree, belonging to families of half-sib offspring of 35 bulls. Ultrasound measurements were used to estimate the BFT and REA when the animals were approximately 18 months of age. Ultrasound images were taken at the cross section of the longissimus muscle area, between the 12th and 13th ribs.

DNA extraction

Blood (5 mL) was collected in vacuum collection tubes from all animals by venipuncture. Extraction of DNA was performed from isolated leukocytes, by a salting out procedure (Regitano, 2001). Where possible, semen samples were collected from sires, for the purpose of parentage confirmation.

SNP population genotyping

Animals were genotyped by restriction fragment length polymorphism-polymerase chain reaction (RFLP-PCR), following previously described methodology (Table 1). For the FABP4 gene, new primers were designed (F: 5'-AATACACACACACACACCTGCTC-3' and R: 5'-AATACACACA CACACACCTGCTC-3').

Table 1. Genes and SNPs analyzed; respective locations and citations.

Gene	SNP	Location	Reference	Animals (N)
Leptin	c.143+808C>T	Intron 2	Liefers et al. (2002)	497
PPARGC1A	c.1892+19T>C	Intron 9	Weikard et al. (2005)	595
PSMC1	c.130+86A>G	Intron 9	Guo et al. (2008)	642
CRH	g.9657C>T	Promoter	Wibowo et al. (2007)	645
FABP4	c.220A>G	Exon 2	Cho et al. (2008)	555

Statistical analysis

Associations between marker genotypes and phenotypes were analyzed under an animal model using the restricted maximum likelihood method (REML), and the ASREML software, developed by Gilmour et al. (2000). Contemporary groups (CG) consisted of animals born in the same year, herd, genetic group (CA or MA), and sex. Contemporary groups with less than two individuals were excluded from analysis; using these criteria, 30 CGs were created. For analysis, CG and marker genotypes were fitted as fixed effects and animal age at measurement as a covariate (linear) effect; direct additive genetic and residual effects were also included. The inverse of the genetic relationship matrix contained 4089 different animals.

Analyses were performed individually for each of the five markers. The statistical model used was: $y = X\beta + Za + e$, where y was the observation vector; X the incidence matrix, which relates records to fixed effects; β was the fixed effects vector (contemporary group, age and genotypes); Z, the incidence matrix, which relates records to random genetic effects; a, the vector of random genetic effects, representing the breeding value of animals; and e, the error vector.

When a significant ($P \leq 0.05$) marker genotype effect was observed, the effect of allele substitution was estimated by replacing the genotype effect by covariates representing the number of copies of each allele in the genotype. The percentage of phenotypic variance explained by markers with a significant effect ($P \leq 0.05$) in association analysis was calculated as described by Schenkel (2005), assuming estimated allele frequencies for the markers, and using the estimated additive (a = 1/2 homozygous genotype 1 - 1/2 homozygous genotype 2) and dominance deviation (d = heterozygous genotype - [1/2 homozygous genotype 1 + 1/2 homozygous genotype 2]) effects for the alleles. The percentage of phenotypic variation explained by markers that showed association with traits studied was calculated using the standard formula of Falconer and Mackay (1996): $\%V = 100 \times (2pq\,[a + d(q - p)]2 + [2pqd]2)/\sigma 2p)$, where %V is the percentage of phenotypic variation explained by the SNP, and $\sigma^2 p$ is the phenotypic variance of the trait.

RESULTS

Backfat thickness measurements had a mean of 1.90 mm with a standard deviation of 0.77 mm, with a coefficient of variation of 40.67%. The REA mean was 46.60 ± 9.19 cm^2 and the coefficient of variation was 19.73%.

All SNPs studied have been previously reported in *Bos taurus* cattle populations (Liefers et al., 2002; Weiudkard et al., 2005; Wibowo et al., 2007; Cho et al., 2008; Guo et al., 2008a). Although crossbred animals were used in the current study, the three possible genotypes for all markers investigated for this Canchim population were observed (Table 2).

Table 2. Allelic and genotypic frequencies of SNP in leptin, *PSMC1*, *PPARGC1A*, *CRH*, and *FABP4* genes.

Gene	Allele	Frequency (%)	Genotype	Frequency (%)
	C	81.97	CC	66.60
Leptin	T	18.03	CT	32.40
			TT	1.00
	A	74.45	AA	58.26
PSMC1	G	25.54	AG	33.80
			GG	7.94
	C	85.63	CC	73.30
PPARGC1A	T	14.36	CT	24.70
			TT	2.00
	C	87.87	CC	77.68
CRH	T	12.12	CT	20.46
			TT	1.86
	A	49.1	AA	23.96
FABP4	G	50.9	AG	50.10
			GG	25.94

Sequence variations in the candidate leptin, *PPARGC1A*, *PSMC1*, *CRH*, and *FABP4* genes, mapped to QTL regions related to production traits, were assessed by genotyping one SNP in each gene. Only one SNP-a non-synonymous mutation in the coding region of *FABP4*-had a significant effect on BFT (Table 3). The estimated allele substitution effect of this marker was 0.1055 mm (Table 4), and this polymorphism accounted for 11.26 and 1.87% of the total genetic and additive variances, respectively. The A allele was associated with reduced BFT, but no other significant associations were found between the markers and traits evaluated (Tables 3 and 5).

Table 3. Results of restricted maximum likelihood analyses of backfat thickness, according to the model for each marker locus.

Effect	Leptin		*PSMC1*		*PPARGC1A*		*CRH*		*FABP4*	
	DF	P value	DF	P value	DF	P value	DF	P value	DF	P value
Mean	1	0.317	1	<0.001	1	0.326	1	<0.001	1	<0.001
CG	12	0.049	29	<0.001	32	<0.001	32	<0.001	29	<0.001
Leptin	2	0.133	-	-	-	-	-	-		
PSMC1	-	-	2	0.412	-	-	-	-		
PPARGC1A	-	-	-	-	2	0.378	-	-		
CRH	-	-	-	-	-	-	2	0.462		
FABP4	-	-	-	-	-	-	-	-	2	0.014
Age	1	<0.001	1	<0.001	1	0.566	1	<0.001	1	<0.001

CG, contemporary groups; DF, degrees of freedom.

Table 4. Results of analysis of the effect of *FABP4* c.220A>G (I74V) SNP allele substitution on backfat thickness in Canchim beef cattle, and estimated regression coefficient to determine contribution of the A allele tophenotype.

	FABP4		Allele effect (backfat thickness mm)
Effect	DF	P value	-
Mean	1	<0.01	-
CG	29	<0.01	-
Allele A	1	0.004	-0.1055
Allele G	-	-	-
Age	1	<0.01	-

CG, contemporary groups; DF, degrees of freedom; P, probability associated with the variance ratio test.

Table 5. Results of restricted maximum likelihood analyses of para rib eye area, according to the model for each marker locus.

Effect	Leptin		*PSMC1*		PPARGC1A		*CRH*		*FABP4*	
	DF	P value	DF	P value	DF	P value	DF	P value	DF	P value
Mean	1	0.294	1	<0.001	1	0.872	1	<0.001	1	<0.001
CG	12	<0.001	29	<0.001	32	<0.001	29	<0.001	29	<0.001
Leptin	2	0.981	-	-	-	-	-	-	-	-
PSMC1	-	-	2	0.861	-	-	-	-	-	-
PPARGC1A	-	-	-	-	2	0.676	-	-	-	-
CRH	-	-	-	-	-	-	2	0.665	-	-
FABP4	-	-	-	-	-	-	-	-	2	0.777
Age	1	0.301	1	<0.001	1	0.395	1	<0.001	1	<0.001

CG, contemporary groups; DF, degrees of freedom.

DISCUSSION

According to Meirelles et al. (2010), who worked with the same population of Canchim breed cattle used in the current study, direct additive variances for BFT and REA were 0.065 and 13.730 and the heritability values were 0.24 ± 0.09 and 0.33 ± 0.09, respectively. Considering the heritability observed for our target traits, we suggest that artificial selection could be applied efficiently to this population. Since these are traits of late onset, information on trait-associated molecular markers provided here will allow early identification of animals with desirable genetic potential for finishing degree and muscularity traits (BFT and REA, respectively).

Several QTL for growth and fat traits, such as marbling and BFT, have been described in BTA14 (Casas et al*.,* 2000; Moore et al., 2003). In fact, more than 30 fat-related QTL have been reported in cattle (Wibowo et al., 2007). Some genes, like *CRH* (Wibowo et al*.,* 2007) and *FABP4* (Michal et al., 2006; Cho et al*.,* 2008), have been selected as candidate genes, mapped to QTL, that may influence these traits. Despite the advent of novel methods such as genome-wide association studies to identify QTL, the candidate genes approach remains the most economically feasible choice to find trait-associated markers for beef cattle producers. Furthermore, the inclusion of information of candidate genes in genome-wide association studies can be an important tool in explaining variations in some characteristics.

A significant effect between the SNP evaluated in *FABP4* and BFT was found, consistent with previously published results. The *FABP4* gene acts to mediate intracellular transport and fatty acid metabolism in adipose tissues. Studies of cattle have associated this gene with BFT (Michal et al., 2006; Cho et al., 2008), marbling (Michal et al., 2006; Avilés et al., 2013), and composition

of palmitoleic and linoleic acids in intramuscular fat (Hoashi et al., 2008). In this study, we evaluated a non-synonymous SNP (c.220A>G (I74V)) located in exon 2, previously described by Cho et al. (2008), who also found a significant effect on BFT. Veneroni-Gouveia et al. (2012) analyzed cattle from the same population used for the current study using a high-density SNP chip, and also observed an association between the region containing *FABP4* and fat thickness, underscoring the likelihood that this gene influences BFT.

The allelic substitution of A by G detected in this study, with the A allele being associated with reduced BFT measures, may be underestimated because BFT was evaluated by ultrasound, which indirectly measures carcass BFT. Cho et al. (2008) found that this SNP in *FABP4* was associated with high mean BFT in the homozygotes AA, contrasting with the allele substitution effect found in the current study. These results can be interpreted as suggesting that this marker is in linkage disequilibrium with QTL, affecting the traits rather than being a causal mutation. Thus, the favorable allele in each breed must be investigated before implementing this polymorphism for marker-assisted selection. Since we did not observe a significant association between this marker and REA, it can be used to improve BFT without influencing muscularity measures in Canchim beef cattle.

The *CHR* gene, also located in BTA14, is related to sugar metabolism and has been indicated as a putative candidate gene that influences meat quality traits. Wibowo et al. (2007) identified five SNPs in this gene (one in the promoter region and four in exon 2) and described a significant association of the SNP in the promoter (g.9657C> T) and two SNPs in exon 2 (c.10718G> C and 10936G > C) with BFT in a population of Wagyu x Limousin F_2 cattle. Additionally, Buchanan et al. (2005) reported an association between polymorphisms in this gene and end-of-test REA. However, conflicting results have also been reported, such as those of Sherman et al. (2008), who did not find an association of two SNPs located in exon 2 of *CRH* with growth, feed efficiency or carcass traits in beef steers. We, also, could not observe a significant association between the SNP evaluated in this gene and any phenotypic record.

The *BTA4* chromosome also has QTL reported for cattle carcass traits, including BFT and REA (Mizoguchi et al*.,* 2006; Takasuga et al*.,* 2007; Yokouchi, et al*.,* 2009; McClure et al*.,* 2010). The leptin gene has been indicated as a major candidate gene located in this QTL, contributing to the variation of BFT (McClure et al., 2010). Buchanan et al. (2002) studied an SNP in exon 2 of the leptin gene and demonstrated its association with carcass fat. In addition, a polymorphism in exon 3 of the leptin gene is related to body weight at 210 days of age and the average daily gain between 3 and 210 days of age in Limousin calves (Kulig and Kmieć, 2009). Guo et al. (2008b) also reported an association between a polymorphism of the leptin receptor and growth traits in Nanyang cattle, in contrast to our results.

Another QTL related to body weight and marbling has been reported on *BTA6* (Mizoguchi et al*.,* 2006; Takasuga et al., 2007). The *PPARGC1A* gene has been pointed out as a candidate gene mapped in this QTL region. In addition to being a positional candidate gene, *PPARGC1A* is also a functional candidate due its influence on energy metabolism. Therefore, we hypothesize that it could also be related to BFT. Many studies have reported associations between polymorphisms in this gene and production traits in different species. In pigs, for example, *PPARGC1A* has been widely studied and found to be a major gene underlying variations in production traits. Stachowiak et al. (2007) reported an SNP in exon 8 of porcine *PPARGC1A* associated with feed conversion ratio, abdominal fat and BFT. In dairy cattle, a significant association between an SNP in intron 9 of *PPARGC1A* and milk fat yield was observed by Weikard et al. (2005). Soria et al. (2009) studied an SNP in exon 8 of the same gene and could not find a significant association between either final live body weight, gain in BFT, kidney fat weight, kidney fat percentage, Warner-Bratzler shear

force at 7 days postmortem, intramuscular fat percentage or meat color, and the SNP studied. In accordance with results presented in the current study, Tizioto et al. (2012) reported no association between the same SNP evaluated in this work, and BFT and REA in a Nellore cattle population.

Proteasomes are distributed in eukaryotic cells in high concentrations. They cleave peptides in an ATP/ubiquitin-dependent process. The *PSMC1* gene plays a fundamental role in many regulatory pathways, and has been associated with variation of a number of production traits in cattle. Guo et al. (2008a) identified an SNP (G/A) in intron 13 of *PSMC1* that was associated with average daily feed intake, average daily gain, finishing average daily gain, body length, ratio of feed to meat, BFT, and loin-muscle area. A QTL mapped in this chromosome (BTA10) is associated with residual feed intake in Hereford x composite double backcross populations (Márquez et al*.,* 2009) and with marbling (Takasuga et al*.,* 2007).

Although some works have reported effects of the leptin, *PPARGC1A*, *PSMC1*, and *CRH* genes on different production traits, as previously discussed, such effects were not observed in the Canchim population used for the present study.

Conflicting results for candidate genes can be attributed to genetic differences among beef cattle populations used in each study, besides environment, management, and diet (Rincker et al*.,* 2006). Reported differences may also be due to differences in the extent of linkage disequilibrium and allele frequencies for causal mutations. These possibilities reinforce the need to test the marker in different populations and environments before implementing marker-assisted selection.

CONCLUSION

Since production traits have a polygenic background, candidate gene studies cannot be expected to explain all trait variation. The results presented here identified *FABP4* as influencing the variation of BFT in a Canchim cattle population, suggesting that this marker could be used to improve accuracy of selection for BFT in this breed. Before being used within other breeding programs, the associated marker, presented here, should be investigated in more breeds and populations, in order to accurately describe its association and phase relationships. This need is reinforced by the lack of associations of markers in the genes leptin, *PPARGC1A*, *PSMC1*, and *CRH* already reported as influencing similar production traits in other breeds.

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