Association of polymorphisms in growth hormone and leptin candidate genes with live weight traits of Brahman cattle

N. Hernández[1], J.C. Martínez-González[1], G.M. Parra-Bracamonte[2], A.M. Sifuentes-Rincón[2], N. López-Villalobos[3,4], S.T. Morris[3], F. Briones-Encinia[1], E. Ortega-Rivas[5], V.I. Pacheco-Contreras[2] and L.A. Meza-García[2]

[1]Facultad de Ingeniería y Ciencias, Universidad Autónoma de Tamaulipas, Centro Universitario Adolfo López Mateos, Ciudad Victoria, Tamaulipas, México
[2]Instituto Politécnico Nacional, Centro de Biotecnología Genómica, Laboratorio de Biotecnología Animal, Reynosa, Tamaulipas, México
[3]Institute of Veterinary, Animal and Biomedical Sciences, Massey University, Palmerston North, New Zealand
[4]Centro Universitario UAEM Temascaltepec, Universidad Autónoma del Estado de México, Temascaltepec, Estado de México, México
[5]Asociación Mexicana de Criadores de Cebú, Tamaulipas, México

Corresponding author: G.M. Parra-Bracamonte
E-mail: gparra@ipn.mx.

Genet. Mol. Res. 15 (3): gmr.15038449
Received January 14, 2016
Accepted July 4, 2016
Published September 2, 2016
DOI http://dx.doi.org/10.4238/gmr.15038449

ABSTRACT. Polymorphisms in candidate genes can produce significant and favorable changes in the phenotype, and therefore are useful for the identification of the best combination of favorable variants

for marker-assisted selection. In the present study, an assessment to evaluate the effect of 11 single nucleotide polymorphisms (SNPs) in candidate genes on live weight traits of registered Brahman cattle was performed. Data from purebred bulls were used in this assessment. The dataset included birth (BW), weaning (WW), and yearling (YW) weights. A panel of 11 SNP markers, selected by their formerly reported or apparent direct and indirect association with live weight traits, was included in an assessment previously confirming their minimum allele frequency (<0.05). Live weights were adjusted BW (aBW), WW (aWW), and YW (aYW) using a generalized linear model, which included the fixed effects of herd and season of birth and the random effect of the sire and year of birth. An SNP in a growth hormone gene (GH4.1) was significantly related to aWW (P = 0.035) with an estimate substitution effect of 3.97 kg (P = 0.0210). In addition, a leptin SNP (LEPg.978) was significantly associated with aYW (P = 0.003) with an estimate substitution effect of 9.57 kg (P = 0.0007). The results suggest that markers GH4.1 and LEPg.978 can be considered as candidate loci for assisted genetic improvement programs in Mexican Brahman cattle.

Key words: *Bos indicus*; GH4.1; Growth traits; LEPg.978; SNP

INTRODUCTION

Genetic improvement is caused by selection of individuals from populations with the best probabilities to produce a favorable change in the trait of interest in the next generation. Genetic management practices have dynamically changed over time, from phenotype and breed conformation selection to performance tests and progeny testing and more recently, to the selection of individuals at an early age based on genomic breeding values (Dekkers and Hospital, 2002).

Growth of calves is represented by the increase in live weight from birth to standard stages of life. The relevance of these traits is determined by their economic relationship with the efficiency and productivity of the production system (Forni et al., 2007). Live weight is influenced by genetic and environmental sources of variation (Krupa et al., 2005). The exact number and identity of the genes promoting variation in live weight traits are unknown; however, through DNA technology, many genes have been identified that are associated with live weight traits in beef cattle (Dekkers and Hospital, 2002; Widmann et al., 2013).

Candidate genes are generally the genes with some known physiological functions related directly or indirectly to the process or performance of the traits of interest. This function may be confirmed by the association between the trait and the actual polymorphisms in the candidate genes. Previous information on the function, activity, and location from genome sequencing data can be used to determine the significant variants in the candidate genes (Zhu and Zhao, 2007).

To date, this approach has partially revealed the genetic architecture of some productive traits and hence, proposed for marker assisted selection in genetic improvement programs of cattle. Some of them include the bovine growth hormone (bGH), associated with carcass fat content and muscle yield, milk yield, and testicular development (Yao et al., 1996; Unanian et al., 2002); the receptor of bGH, associated with a large number of productive traits such as milk yield and composition (Viitala et al., 2006), feed consumption, and feed conversion

efficiency (Banos et al., 2008); and the bGH releasing hormone associated with carcass traits (Cheong et al., 2006). From an interactive network, some of these candidate genes, although not directly related to a determined trait, can have an indirect physiological relationship leading to significant enhancement of a correlated response in another trait (Paredes-Sánchez et al., 2015). Different variants of casein have been related to milk yield and composition and protein content (Caroli et al., 2009). Allegedly, the segregation of variation in these genes might be related through the regulation of milk composition to promote growth through enhanced nutrition from milk composition during the pre-weaning stage in calves (Brown and Brown, 2002; Pacheco et al., 2015). Similarly, leptin gene variation has been reported to be associated with milk yield, live weight, energy balance, feed consumption, and carcass fat content (Buchanan et al., 2002; Liefers et al., 2002; Madeja et al., 2004).

In theory, polymorphisms in such candidate genes can produce significant and favorable changes in phenotype, and therefore can be used to identify the best combination of favorable variants in candidate genes for marker-assisted selection. The availability of such DNA diagnostic testing could be an important tool for genetic improvement (Dekkers, 2004).

The Brahman cattle, a breed of Zebu cattle, is the most popular and widespread breed and widely used in tropical and subtropical regions because of their thermoregulatory ability under high temperatures and humidity, as well as their genetic resistance to diseases and parasites (Hansen, 2004). This breed is maintained as purebred animals but also as crossbred animals with European breeds in meat production systems and dual-purpose systems (McDowell et al., 1996).

The objective of this study was to assess the effect of single nucleotide polymorphisms (SNPs) in candidate genes on live weight traits of registered Brahman bulls from Mexico.

MATERIAL AND METHODS

An 11 SNP panel, located in eight candidate genes related directly and indirectly to live weight and size traits, was considered in order to assess their association with live weight traits in registered and unrelated Brahman bulls (N = 145) from different herds (N = 27) from tropical and subtropical regions of Tamaulipas and Veracruz States of Mexico. Animals included in the study were purebred Brahman bull sire candidates managed under an extensive production system and registered in the Asociación Mexicana de Criadores de Cebú (AMCC) database for breeding control.

Information available on these animals included dates of weighing, live weights at different ages, herd of origin, and sire (N = 90). Live weight traits evaluated were birth weight (BW), weaning weight at 205 days (WW), and yearling weight (YW) from the Weighted Performance Control Program of the AMCC located in Tampico, Tamaulipas, Mexico. The dataset included all the information related to breeding and management of animals included in the study.

Hair follicle samples were obtained and processed for genotyping of the SNP panel by GeneSeek Inc. (Lincoln, NE, USA) in the Sequenom MassARRAY® system platform (iPLEX GOLD; Sequenom, San Diego, CA, USA). For the design of specific primers, the available information on the identity and location of candidate loci was used. As an initial screen, a 44 SNP previously assessed and described panel by Parra-Bracamonte et al. (2014) was genotyped, but only 11 SNPs were maintained for further association analysis (Table 1) excluding monomorphic and minimum allele frequency >0.05 loci.

Table 1. Identification of analyzed SNPs and their minimum allele frequency (MAF) in Mexican Brahman cattle.

Locus	Gene	Region	Allele1/Allele2	AA change	MAF[1]	Reference
GH6.2	GH	Exon 5	A/C		A: 0.12	Yao et al., 1996
bGH-*Hae*III	GH	Intron	C/G		C: 0.12	Unanian et al., 2000
GH4.1	GH	Intron	T/C		C: 0.44	Yao et al., 1996
GHRN528T	GHR	Exon 10	A/C	Asp>Thr	A: 0.49	Blott et al., 2003
GHRH4241	GHRH	5'-UTR	A/T		T: 0.06	Cheong et al., 2006
LGB3984	LGB	Exon 3	G/A	Asp>Val	A: 0.35	Farrell et al., 2004
LGB5263	LGB	Exon 4	C/T	Gly>Ala	T: 0.36	Kamiński et al., 2005
CSN1S1-175	CSN1S1	5'-region	A/G		G: 0.31	Kuss et al., 2005
PRL8398	PRL	Exon 4	G/A		G: 0.47	Brym et al., 2005
V30A	CYP11B1	5'-region, Exon I	C/T	Val>Ala	T: 0.47	Kaupe et al., 2007
LEPg.978	LEP	Intron	C/T		T: 0.15	Orrù et al., 2011

[1]This study. GH: growth hormone, GHR: GH receptor, GHRH: GH releasing hormone, LGB: lactoglobulin beta, CSN1S1: casein alpha 1, PRL: prolactin, CYP11B1: 11 β-hydroxylase, LEP: leptin.

Statistical analysis included the verification of linkage disequilibrium among selected SNPs using the GENEPOP software (Rousset, 2008). A first linear model was fitted using a model as follows:

$$Y_{ijkl} = \mu + T_i + AN_j + H_k + EN_l + \varepsilon_{ijkl} \quad \text{(Equation 1)}$$

where Y_{ijkl} = BW, WW, and YW; μ = overall mean; T_i = random effect of ith sire; AN_j = random effect of jth year of birth; H_k = fixed effect of kth herd; EN_l = fixed effect of lth season of birth (dry, rain); and, ε_{ijkl} = random residual error.

Posteriorly, from the first model (R^2_{BW} = 0.93; R^2_{WW} = 0.86; R^2_{YW} = 0.89), residual errors were considered as adjusted phenotypes of BW (aBW), WW (aWW205), and YW (aYW) and analyzed with a linear model to estimate the effect of genotypes in selected SNPs. This model was as follows:

$$Y_{ij} = \mu + G_i + \varepsilon_{ij} \quad \text{(Equation 2)}$$

where Y_{ij} = aBW, aWW205, and aYW; μ = overall mean; G_i = fixed effect of ith genotype in a selected locus; and ε_{ij} = random residual error. Genotype means were compared by the Tukey method with an alpha = 0.05. The allelic substitution effect of significant loci was estimated using genotype dummy variables as covariates in the linear model. All analyses were conducted using the SAS software (SAS Institute, Cary, NC, USA).

RESULTS AND DISCUSSION

Eleven SNPs were assessed for their relationship with live weight traits of Brahman bulls. From the evaluated SNPs, only two showed significant effects ($P \leq 0.03$) on different live weight traits (Table 2). Some of the loci assessed here were previously included and evaluated for their association with birth weight traits in a Charolais cattle population (Parra-Bracamonte et al., 2014); only two growth hormone receptor SNPs were found significantly associated with this trait.

Table 2. P values estimated for association analysis of assessed SNPs on adjusted live weight traits of Brahman cattle.

Locus	aBW	aWW	aYW
GH6.2	0.910	0.786	0.189
bGH-*Hae*III	0.911	0.952	0.289
GH4.1	0.909	**0.035**	0.873
GHRN528T	0.123	0.306	0.087
GHRH4241	0.777	0.983	0.846
LGB3984	0.130	0.054	0.632
LGB5263	0.092	0.096	0.639
CSN1S1-175	0.634	0.898	0.946
PRL8398	0.710	0.788	0.866
V30A	0.8976	0.157	0.394
LEPg.978	0.649	0.250	**0.003**

aBW = adjusted birth weight; aWW = adjusted weaning weight; aYW = adjusted yearling weight. Significant associations are in bold.

Although some weak associations were observed, i.e., LGB5263 from lactoglobulin genes with aBW (P = 0.092), LGB3984 and LGB5263 from lactoglobulin with aWW (P < 0.10), and GHRN528T from the GH receptor with aYW (P = 0.087), only GH4.1 from the GH gene and LEPg.978 from the leptin gene had a statistically significant effect on aWW and aYW, respectively (P ≤ 0.03; Table 2).

The significant association of the GH4.1 SNP with aWW (Table 3) revealed that the favorable genotype was CC with an allele substitution effect of 3.97 kg (P = 0.0210; Table 3). This polymorphism is located in bGH, which is 1800 bp long with 5 exons and 4 introns, on chromosome 19, and produces a protein of 191 amino acids with a molecular weight of 22 kDa (Vukasinovic et al., 1999). This pituitary gland-borne protein is one of the most important hormones involved in the process of production and composition of the milk; thus, it has an important function during lactation and growth processes (Secchi and Borromeo, 1997). The GH4.1 polymorphism is a transition variation of C/T, located in nucleotide position 1547 of intron III, described as bGH-*Msp*I after the restriction site used for its genotyping (Yao et al., 1996).

Table 3. Genotypic least square means and allelic substitution effect (α) of associated polymorphisms on adjusted weaning and yearling weights (kg) of Brahman cattle.

Locus	Trait	Genotype least square means ± SE (N)			α
		CC	CT	TT	
GH4.1	aWW	2.57 ± 2.15^{a} (39)	0.893 ± 1.63^{ab} (67)	-6.122 ± 2.80^{b} (23)	3.97*
LEPg.978	aYW	2.41 ± 1.80^{a} (97)	-0.291 ± 3.68^{ab} (24)	-24.853 ± 6.25^{b} (8)	9.57**

aWW = adjusted weaning weight, aYW = adjusted yearling weight. Means with different letters are significantly different within a trait (P < 0.05). *P = 0.0210, **P = 0.0007.

The GH4.1 polymorphism has been reported for its utility in *Bos taurus indicus* versus *Bos taurus taurus* divergence studies, since a differential segregation frequency for specific alleles exists among these subspecies (Lagziel et al., 2000). However, in populations of Zebu cattle, this polymorphism showed an equilibrated genotypic distribution allowing further association analyses (Unanian et al., 2000; Beauchemin et al., 2006).

Unanian et al. (2000) assessed the effect of the *Msp*I polymorphism on growth traits for the first time in a Nellore cattle population and documented a significant effect on the average daily weight gain from weaning to 15 months with DD (equivalent to *Msp*I- or GG

genotypes) as the favorable genotype. Similarly, Arango et al. (2014) evaluated the effect of *Msp*I in a Holstein population and found a significant effect on weight at first estrus and first calving in heifers; the MspI+ allele was found to produce a decreasing effect on these weight traits. However, Beauchemin et al. (2006) assessed this polymorphism but did not find a significant relationship with live weight and carcass traits in Brahman steers, concluding that this polymorphism is not predictive for these traits.

The *Msp*I polymorphism has been widely studied and is frequently related positively to milk production traits. Some studies have shown that *Msp*I+, the equivalent variant of the C allele, has a positive effect on milk yield and composition traits (Yao et al., 1996; Zhou et al., 2005; Pawar et al., 2007; Rincón et al., 2013). However, there are some contradictory results indicating the positive effect of the -/- genotype on milk yield (Rincón et al., 2013).

An indirect relationship among dam milk components provided to the calves through the milk may be a possible hypothesis. Since milk yield maintains a strong correlation with body size and yield traits, it may potentially have a positive relationship with growth traits. Although no consistent allele effect has been found in the literature, it is clear that the significant effect of this locus needs more attention. In populations where validated evidence is available, the inclusion of this locus in assisted selection programs might be possible. The significant substitution effect of the GH4.1 SNP found in the present study suggests that this marker can be used as a genetic marker for assisted selection for weaning weight in local Brahman populations.

In contrast, the polymorphism LEPg.978 (rs29004484), significantly associated with aYW ($P = 0.003$), is located in leptin intron 1. Leptin, an adipocyte-derived hormone, is related to different physiological functions and associated with some productive and reproductive traits in livestock (Mácajová et al., 2004). It is considered as a predictor of live weight, scrotal circumference, and reproductive hormones (Thomas et al., 2002). In the present study, the C allele produced a substitution effect of 9.7 kg ($P = 0.0007$) with a significant difference between the CC genotype in comparison to heterozygous and homozygous (CT and TT) genotypes (Table 3).

Orrù et al. (2011) first reported this polymorphism to be significantly related to desaturation of fatty acids into monounsaturated fatty acids resulting in its influence on the composition of muscle fat in Simmental bulls. The study by Corva et al. (2009) reported no significant association between the LEPg.978 polymorphism and live weight traits in Brangus steers. The effect of different closely related leptin polymorphisms has been evaluated on several traits and species. Some studies associate these polymorphisms with milk yield, feed intake, and live weight (Liefers et al., 2002), carcass fat (Buchanan et al., 2002), and milk and protein yield (Madeja et al., 2004) in Holstein heifers. Although a significant effect on yearling weight was found in the present study, no direct relationship with this gene can be proposed; further validation might corroborate the putative effect of LEPg.978 and its possible linkage with other loci.

A candidate gene approach may provide relevant information directing the search into previously reported genome regions to have significant associations in other populations (Zhu and Zhao, 2007). However, validation of previous evidence is important for achieving continuous genetic improvement of local cattle populations. Since sampled animals are purebred registered sires, it is important to remark their potential use in genetic improvement programs allowing segregation of identified favorable alleles by introgression into commercial productive herds.

In conclusion, single nucleotide polymorphisms GH4.1 and LEPg.978 greatly influence weaning live weight and yearling live weight of Brahman cattle, respectively. This new evidence supports these SNPs as candidate polymorphisms for assisted selection of live weight traits. Further validation is required in other breeds or particular populations for extensive use in genetic improvement programs.

Conflicts of interest

The authors declare no conflict of interest.

ACKNOWLEDGMENTS

Corresponding author want to thank Instituto Politécnico Nacional for its support through the funding of SIP20150746 project.

REFERENCES

Arango J, Echeverri JJ and López A (2014). Association between a polymorphism in intron 3 of the bovine growth hormone gene and growth traits in Holstein heifers in Antioquia. *Genet. Mol. Res.* 13: 6191-6199. http://dx.doi.org/10.4238/2014.August.15.1

Banos G, Woolliams JA, Woodward BW, Forbes AB, et al. (2008). Impact of single nucleotide polymorphisms in leptin, leptin receptor, growth hormone receptor, and diacylglycerol acyltransferase (DGAT1) gene loci on milk production, feed, and body energy traits of UK dairy cows. *J. Dairy Sci.* 91: 3190-3200. http://dx.doi.org/10.3168/jds.2007-0930

Beauchemin VR, Thomas MG, Franke DE and Silver GA (2006). Evaluation of DNA polymorphisms involving growth hormone relative to growth and carcass characteristics in Brahman steers. *Genet. Mol. Res.* 5: 438-447.

Blott S, Kim JJ, Moisio S, Schmidt-Küntzel A, et al. (2003). Molecular dissection of a quantitative trait locus: a phenylalanine-to-tyrosine substitution in the transmembrane domain of the bovine growth hormone receptor is associated with a major effect on milk yield and composition. *Genetics* 163: 253-266.

Brown MA and Brown Jr AH (2002). Relationship of milk yield and quality to preweaning gain of calves from Angus, Brahman and reciprocal-cross cows on different forage systems. *J. Anim. Sci.* 80: 2522-2527.

Brym P, Kamiński S and Wójcik E (2005). Nucleotide sequence polymorphism within exon 4 of the bovine prolactin gene and its associations with milk performance traits. *J. Appl. Genet.* 46: 179-185.

Buchanan FC, Fitzsimmons CJ, Van Kessel AG, Thue TD, et al. (2002). Association of a missense mutation in the bovine leptin gene with carcass fat content and leptin mRNA levels. *Genet. Sel. Evol.* 34: 105-116. http://dx.doi.org/10.1186/1297-9686-34-1-105

Caroli AM, Chessa S and Erhardt GJ (2009). Invited review: milk protein polymorphisms in cattle: effect on animal breeding and human nutrition. *J. Dairy Sci.* 92: 5335-5352. http://dx.doi.org/10.3168/jds.2009-2461

Cheong HS, Yoon DH, Kim LH, Park BL, et al. (2006). Growth hormone-releasing hormone (GHRH) polymorphisms associated with carcass traits of meat in Korean cattle. *BMC Genet.* 7: 35. http://dx.doi.org/10.1186/1471-2156-7-35

Corva PM, Fernández Macedo GV, Soria LA, Papaleo Mazzucco J, et al. (2009). Effect of leptin gene polymorphisms on growth, slaughter and meat quality traits of grazing Brangus steers. *Genet. Mol. Res.* 8: 105-116. http://dx.doi.org/10.4238/vol8-1gmr556

Dekkers JCM (2004). Commercial application of marker- and gene-assisted selection in livestock: strategies and lessons. *J. Anim. Sci.* 82 E-Suppl: E313-E328.

Dekkers JCM and Hospital F (2002). The use of molecular genetics in the improvement of agricultural populations. *Nat. Rev. Genet.* 3: 22-32. http://dx.doi.org/10.1038/nrg701

Farrell HM Jr, Jimenez-Flores R, Bleck GT, Brown EM, et al. (2004). Nomenclature of the proteins of cows' milk - sixth revision. *J. Dairy Sci.* 87: 1641-1674. http://dx.doi.org/10.3168/jds.S0022-0302(04)73319-6

Forni S, Piles M, Blasco A, Varona L, et al. (2007). Analysis of beef cattle longitudinal data applying a nonlinear model. *J. Anim. Sci.* 85: 3189-3197. http://dx.doi.org/10.2527/jas.2006-677

Hansen PJ (2004). Physiological and cellular adaptations of zebu cattle to thermal stress. *Anim. Reprod. Sci.* 82-83: 349-360. http://dx.doi.org/10.1016/j.anireprosci.2004.04.011

Kamiński S, Ahman A, Ruść A, Wójcik E, et al. (2005). MilkProtChip - a microarray of SNPs in candidate genes associated with milk protein biosynthesis - development and validation. *J. Appl. Genet.* 46: 45-58.

Kaupe B, Brandt H, Prinzenberg EM and Erhardt G (2007). Joint analysis of the influence of CYP11B1 and DGAT1 genetic variation on milk production, somatic cell score, conformation, reproduction, and productive lifespan in German Holstein cattle. *J. Anim. Sci.* 85: 11-21. http://dx.doi.org/10.2527/jas.2005-753

Krupa E, Oravcová M, Polák P, Huba J, et al. (2005). Factors affecting growth traits of beef cattle breeds raised in Slovakia. *Czech J. Anim. Sci.* 50: 14-21.

Kuss AW, Gogol J, Bartenschlager H and Geldermann H (2005). Polymorphic AP-1 binding site in bovine CSN1S1 shows quantitative differences in protein binding associated with milk protein expression. *J. Dairy Sci.* 88: 2246-2252. http://dx.doi.org/10.3168/jds.S0022-0302(05)72900-3

Lagziel A, DeNise S, Hanotte O, Dhara S, et al. (2000). Geographic and breed distribution of an Msp I PCR-RFLP in the bovine growth hormone (bGH) gene. *Anim. Genet.* 31: 210-213. http://dx.doi.org/10.1046/j.1365-2052.2000.00622.x

Liefers SC, te Pas MF, Veerkamp RF and van der Lende T (2002). Associations between leptin gene polymorphisms and production, live weight, energy balance, feed intake, and fertility in Holstein heifers. *J. Dairy Sci.* 85: 1633-1638. http://dx.doi.org/10.3168/jds.S0022-0302(02)74235-5

Mácajová M, Lamosová D and Zeman M (2004). Role of leptin in farm animals: a review. *J. Vet. Med. A Physiol. Pathol. Clin. Med.* 51: 157-166. http://dx.doi.org/10.1111/j.1439-0442.2004.00619.x

Madeja Z, Adamowicz T, Chmurzynska A, Jankowski T, et al. (2004). Effect of leptin gene polymorphism on breeding value for milk production traits. *J. Dairy Sci.* 87: 3925-3927. http://dx.doi.org/10.3168/jds.S0022-0302(04)73531-6

McDowell RE, Wilk JC and Talbott CW (1996). Economic viability of crosses of *Bos taurus* and *Bos indicus* for dairying in warm climates. *J. Dairy Sci.* 79: 1292-1303. http://dx.doi.org/10.3168/jds.S0022-0302(96)76484-6

Orrù L, Cifuni GF, Piasentier E, Corazzin M, et al. (2011). Association analyses of single nucleotide polymorphisms in the LEP and SCD1 genes on the fatty acid profile of muscle fat in Simmental bulls. *Meat Sci.* 87: 344-348. http://dx.doi.org/10.1016/j.meatsci.2010.11.009

Pacheco CVI, Parra BGM, López BLA, Moreno MVR, et al. (2015). Milk composition and its relationship with weaning weight in Charolais cattle. *Rev. Bras. Zootec.* 44: 207-212. http://dx.doi.org/10.1590/S1806-92902015000600002

Paredes-Sánchez FA, Sifuentes-Rincón AM, Segura Cabrera A, García Pérez CA, et al. (2015). Associations of SNPs located at candidate genes to bovine growth traits, prioritized with an interaction networks construction approach. *BMC Genet.* 16: 91. http://dx.doi.org/10.1186/s12863-015-0247-3

Parra-Bracamonte GM, Lopez-Villalobos N, Sifuentes-Rincon AM, Morris S, et al. (2014). Single and composite influence of growth-related candidate gene polymorphisms on additive genetic variation of birth weight in Charolais beef cattle. *Trop. Anim. Health Prod.* 46: 509-512. http://dx.doi.org/10.1007/s11250-013-0520-2

Pawar RS, Tajane KR, Joshi CG, Rank DN, et al. (2007). Growth hormone gene polymorphism and its association with lactation yield in dairy cattle. *Indian J. Anim. Sci.* 77: 884-888.

Rincón JC, López-Herrera A and Echeverri JJ (2013). Effect of two single nucleotide polymorphisms on milk yield and composition. *Genet. Mol. Res.* 12: 995-1004. http://dx.doi.org/10.4238/2013.April.2.15

Rousset F (2008). genepop'007: a complete re-implementation of the genepop software for Windows and Linux. *Mol. Ecol. Resour.* 8: 103-106. http://dx.doi.org/10.1111/j.1471-8286.2007.01931.x

Secchi C and Borromeo V (1997). Structure and function of bovine growth hormone. Bovine growth hormone as an experimental model for studies of protein-protein interactions. *J. Chromatogr. B Biomed. Sci. Appl.* 688: 161-177. http://dx.doi.org/10.1016/S0378-4347(96)00296-4

Thomas MG, Enns RM, Hallford DM, Keisler DH, et al. (2002). Relationships of metabolic hormones and serum glucose to growth and reproductive development in performance-tested Angus, Brangus, and Brahman bulls. *J. Anim. Sci.* 80: 757-767.

Unanian MM, Barreto CC, Freitas ARD, Cordeiro CMT, et al. (2000). Associations between growth hormone gene polymorphism and weight traits in Nellore bovines. *Rev. Bras. Zootec.* 29: 1380-1386. http://dx.doi.org/10.1590/S1516-35982000000500016

Unanian MM, Chaves C, Torres CC, Ribeiro FA, et al. (2002). Possible associations between bovine growth hormone gene polymorphism and reproductive traits. *Braz. Arch. Biol. Technol.* 45: 293-299. http://dx.doi.org/10.1590/S1516-89132002000300007

Viitala S, Szyda J, Blott S, Schulman N, et al. (2006). The role of the bovine growth hormone receptor and prolactin receptor genes in milk, fat and protein production in Finnish Ayrshire dairy cattle. *Genetics* 173: 2151-2164. http://dx.doi.org/10.1534/genetics.105.046730

Vukasinovic N, Denise SK and Freeman AE (1999). Association of growth hormone loci with milk yield traits in Holstein bulls. *J. Dairy Sci.* 82: 788-794. http://dx.doi.org/10.3168/jds.S0022-0302(99)75297-5

Widmann P, Reverter A, Fortes MR, Weikard R, et al. (2013). A systems biology approach using metabolomic data reveals genes and pathways interacting to modulate divergent growth in cattle. *BMC Genomics* 14: 798. http://dx.doi.org/10.1186/1471-2164-14-798

Yao J, Aggrey SE, Zadworny D, Hayes JF, et al. (1996). Sequence variations in the bovine growth hormone gene characterized by single-strand conformation polymorphism (SSCP) analysis and their association with milk production traits in Holsteins. *Genetics* 144: 1809-1816.

Zhou GL, Liu HG, Liu C, Guo SL, et al. (2005). Association of genetic polymorphism in GH gene with milk production traits in Beijing Holstein cows. *J. Biosci.* 30: 595-598. http://dx.doi.org/10.1007/BF02703558

Zhu M and Zhao S (2007). Candidate gene identification approach: progress and challenges. *Int. J. Biol. Sci.* 3: 420-427. http://dx.doi.org/10.7150/ijbs.3.420