

Genome-Wide Association Analysis for Liveweight Traits in Braunvieh Cattle

José Luis Zepeda-Batista

Universidad de Colima

Rafael Nuñez-Domínguez

Universidad Autonoma Chapingo

Rodolfo Ramírez-Valverde

Universidad Autonoma Chapingo

Agustín Ruíz-Flores

Universidad Autonoma Chapingo

Francisco Joel Jahuey-Martínez

Universidad Autonoma de Chihuahua

Gaspar Manuel Parra-Bracamonte (✉ gparra@ipn.mx)

Instituto Politecnico Nacional <https://orcid.org/0000-0002-9327-2042>

Research Article

Keywords: Association, candidate gene, growth, quantitative trait loci, single nucleotide polymorphism

Posted Date: May 10th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-485005/v1>

License:   This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Abstract

A genome-wide association study (GWAS) for liveweight traits of Braunvieh cattle was performed. The study included 300 genotyped animals by the GeneSeek® Genomic Profiler Bovine LDv.4 panel; after quality control, 22,734 SNP and 276 animals were maintained in the analysis. The examined phenotypic data considered birth, weaning, and yearling weights. The association analysis was performed using the principal components method via the *egscore* function of the GenABEL version 1.8-0 package in the R environment. The marker rs133262280 located in BTA 22 was associated with birth weight, and two SNPs were associated with weaning weight, rs43668789 (BTA 11) and rs136155567 (BTA 27). New QTL associated with these liveweight traits and four positional and functional candidate genes potentially involved in variations of the analyzed traits were identified. The most important genes in these genomic regions were *MCM2* (minichromosome maintenance complex component 2), *TPRA1* (transmembrane protein adipocyte associated 1), *GALM* (*galactose mutarotase*), and *NRG1* (neuregulin 1), with relationships with embryonic cleavage, bone and tissue growth, cell adhesion, and organic development. This study is the first to present a GWAS conducted in Braunvieh cattle in Mexico and represents a basis for future research. Further analyses of found associated regions will clarify its contribution to the genetic basis of growth-related traits.

Introduction

The identification of causal genetic variability is one of the main goals in the genetic improvement of cattle. Commonly, liveweight traits are used as the primary selection criterion in cow-calf production systems in Mexico (Jahuey-Martínez et al., 2016). Usually, farms use these traits as efficiency and meat potential production indicators, and they are used for genetic evaluations in most of the registered breeds (Parra-Bracamonte et al., 2015).

Braunvieh is a worldwide cattle breed used in the beef industry that has been used in both specialized beef and dual-purpose production herds (Orantes-Zebadúa et al., 2014; Phillips et al., 2009). Due to its initial dual-purpose origin, most of the available information about the Braunvieh deals with dairy production traits. However, during the last 15 years, Braunvieh cattle have been selected and genetically improved for beef production traits (Chin-Colli et al., 2016; Phillips et al., 2009). In Mexico, Braunvieh is one of the breeds most used for the beef production industry either as purebred or in crosses with *Bos indicus* cattle (AMCGSR, 2017, Orantes-Zebadúa et al., 2014). However, despite its extensive use, there is scarce information on the breed's productive performance, and the available information is mainly related to growth traits coming from genetic evaluations or isolated studies (AMCGSR, 2017; Chin-Colli et al., 2016; Silva et al., 2002). The selection, management, and genetic improvement programs of the Braunvieh cattle could be enhanced using high-throughput genotyping technologies.

The use of microarrays of thousands of SNP markers in genome-wide association studies (GWAS) has allowed discovering the genetic basis of complex traits and diseases by detecting genotype-phenotype associations in a group of individuals (Tian et al., 2020). GWAS approaches have confirmed many QTL for growth traits in beef and crossbred cattle (Jahuey-Martínez et al., 2016; Lu et al. 2013; Martínez et al., 2016), some of which have been used as the basis for the search for specific causal variation (Takasuga, 2016) and a better understanding of the genetic architecture of these complex traits. Many of these QTL, genomic regions and genes, affecting production traits in beef cattle has been reported (Jahuey et al., 2016; Londoño-Gil et al., 2021; Purfield et al., 2015; Rolf et al., 2012), but most of the association studies focused on specialized beef breeds and only a few researches have been implemented in breeds such as Braunvieh (Guo et al., 2012; Maxa et al., 2012). The present study is aimed to perform a GWAS to identify QTLs and candidate genes related to liveweight traits in a Braunvieh cattle population.

Materials And Methods

Approval from the ethical committee for animal care and use was unnecessary because the samples used in this study consisted of hair follicles, and all analyses were performed using pre-existing databases.

Population and phenotypic data

Hair follicle samples from 236 females and 64 males registered in the Mexican Braunvieh Cattle Association database was collected. The cattle were born between 2000 and 2015. This population came from herds located in the east, west, and central highlands of Mexico. Herds from west and east were raised under extensive production systems, while central highlands herds were under intensive regimens. The sampled population's genetic background included Austrian, Swiss, Canadian, American, and Mexican animals. Phenotypic data were provided by the breeding association and included records of birth weight (BWT, kg), weaning weight (WWT, kg), yearling weight (YWT, kg). Weaning and yearling weights were adjusted to perform the GWAS analysis. Table 1 shows the descriptive statistics for each trait.

Table 1
Descriptive statistics for studied live weight traits (kg) of Braunvieh Cattle.

Trait ¹	<i>n</i>	<i>n</i> (QC) ²	Mean	SD	Minimum	Maximum
BW	300	266	38.007	4.067	22	50
WW	300	263	212.399	27.426	128	308
YW	300	244	313.165	45.473	176	440

¹BW: birth weight; WW: weaning weight; YW = yearling weight.
²*n*(QC) = *n* after quality control.

Genotyping and quality control

The animals were genotyped using 30,125 SNP markers from the GeneSeek® Genomic Profiler Bovine LDv.4 panel (Neogen Corp. Lincoln, NE, USA). Before association analysis, the genotypic data quality was verified using the SNPQC program (Gondro et al., 2014). The genotypes were considered successful if they presented a GenCall value greater than 0.50, and all SNPs with lower values were discarded (*n* = 1623). Those SNPs that were monomorphic (*n* = 3604), presented call rates of less than 90% (*n* = 1290) or minor allele frequencies < 0.01 (*n* = 1325), or deviated from Hardy-Weinberg equilibrium according to Fisher's exact test and exhibited *P*-values > 1×10^{-15} (*n* = 0) were also eliminated. Besides, SNPs with unknown coordinates in the assembly of the bovine genome UMD v3.1 (Zimin et al., 2009) (*n* = 1484) and SNPs that were not located on autosomal chromosomes (*n* = 1820) were discarded.

Samples were also eliminated if they exhibited call rates of less than 80% (*n* = 0) or levels of heterozygosity (HE) above 3 SD (*n* = 1), considering that the mean and SD of the observed HE were 0.32 and 0.019, respectively. A Pearson correlation was computed for detecting potentially duplicate samples, considering a maximum of *r* = 0.98, according to their genotype information obtaining an average of *r* = 0.817 and minimum and maximum values of 0.66 and 0.90, respectively. A total of 22,734 SNPs and 276 samples passed the quality control procedure and were retained for further analysis. Quality control and subsequent analyses were performed in the R environment.

Population structure and association analysis

Population structure was analyzed, calculating first a genomic relationships matrix using the information on genotypes according to Van Raden (2008), besides performing a singular value decomposition and a principal

components (PC) analysis.

The PC analysis indicated that the first two PCs explained 28.6% of the variance in the data. Therefore, the genome-wide association analysis was performed using the PC method proposed by Price et al. (2006). For this analysis, the egsgscore function from the GenABEL package (Aulchenko et al., 2007) was employed. This function accounts for population stratification and uses the genomic kinship matrix to derive axes of genetic variation, and then both the phenotypes and genotypes are adjusted onto these axes.

A linear model for each trait was fitted, including the first two PC as covariates. For the analysis of BWT, the model also included the contemporary group (CG) and the linear and quadratic effects of cow age at the birth and weaning of her calf. The CG included herd, sex, year, and calving season. The statistical model used to adjust the other traits only included the CG and the PCs as covariates; cow age was excluded because it was not significant in the previous analysis. Finally, the association between corrected genotypes and phenotypes was assessed via correlation. P -values were obtained by calculating the square of the correlation multiplied by $(N-K-1)$, where N was the number of genotyped individuals, and K was the number of PCs.

Minimum allele frequencies, allele substitution effect (β), and percentage of phenotypic variance explained by the SNP were estimated. SNP with P -values $< 5 \times 10^{-5}$ were considered significantly associated with studied traits. The proportion of phenotypic variance explained by the SNPs was estimated by dividing the X^2 value for a df by the number of individuals used to analyze each SNP marker, followed by multiplication by 100. All described analyses and estimations were performed using the GenABEL package (Aulchenko et al., 2007).

Analysis of genomic regions with significant SNPs

The closest genes to significant markers and those located within a 250-kb window on both SNP location sides were identified. The list of genes was obtained using the `snp2gene.LD` function from the Postgwas package (Hiersche et al., 2013). Distance between SNPs and genes was calculated as the difference between the marker position and the beginning or end of the gene, according to coordinates from bovine genome assembly UMD v3.1. Gene functions were investigated in the UniProt database (The UniProt Consortium, 2021).

Annotations from humans or mice were used when there was no information on the genes in cattle. Genes were considered functional and positional candidates if they were biologically related to the trait under study, supported by experimental evidence in the literature. Finally, we determined whether significant SNPs mapped against QTLs previously associated with growth-related traits such as BW, carcass, and reproduction traits, deposited in the cattle AnimalQTLdb (Hu et al., 2013). For this purpose, SNP positions according to the Btau4.6 genome sequence were used because many of the previously reported QTLs had no well-defined positions in the bovine genome assembly UMD v3.1.

Results

A total of 30,125 SNP markers from the GeneSeek® Genomic Profiler Bovine LD v4 microarray panel (Neogen Corp. Lincoln, NE, USA) were used for association with live weight traits of Braunvieh cattle. On average, 1,004 SNP markers were evaluated in each BTA. *Bos taurus* chromosomes 1 and 27 exhibited the highest (1602) and lowest (512) SNP numbers. The average distance between adjacent SNP was 87,641 bp, the minimum distance (0 bp) between adjacent SNP were found on BTA 1, 6, 7, 12, 17, 18, 22, 25, 26, 28, and 29, while the maximum distance (1,962,000 bp) was found on BTA 6.

According to the significance threshold considered ($P < 5 \times 10^{-5}$), 3 SNP were associated with the live weight traits (Table 2, Fig. 2). The rs133262280 located in BTA22 was associated with BW, showing an allelic substitution effect of 0.320 ± 0.02 kg. The rs43668789 and rs136155567, located in BTA11 and 27, respectively, were associated with WW. These markers showed allelic substitution effects of -9.590 ± 0.25 and 1.110 ± 0.72 kg, respectively (Table 2).

Table 2
Parameters and statistics of SNP associated with liveweight traits of Braunvieh cattle¹.

Trait	SNP ID ²	BTA	UMD ³ bp	Btau4.6, ⁴ bp	Allele	MAF ⁵	β^6	SE	Var% ⁷	P-value
BW	rs133262280	22	60,759,211	127,745,473	C/T	0.18	0.320	0.02	0.1	2.74e-5
WW	rs43668789	11	21,312,462	22,502,811	C/T	0.17	-9.590	0.25	2.98	5.28e-5
	rs136155567	27	27,056,807	29,944,194	A/G	0.20	1.110	0.72	1.1	1.27e-5

¹BW = birth weight; WW = weaning weight.
²ID = identification.
³UMD version 3.1 (Zimin et al., 2009).
⁴Elsik et al. (2016).
⁵MAF = minimum allele frequency
⁶ β = allele substitution effect
⁷Var% = phenotypic variance explained by the SNP.

Figure 2 shows the Manhattan plots in which the $-\log_{10}$ transformations of the P-values are plotted for each GWAS. QTLs previously associated with growth-related traits are shown in Table 3. Tables 4 to 6 show complete descriptions, including the identifier number and exact location identified in this study.

Table 3
Previously reported QTL1 found near the SNP associated with growth traits of Braunvieh cattle.

Trait_SNP ID ² _BTA_Mb	QTL	QTL ID	QTL in Btau4.6, ³ bp	QTL reference
BW_rs133262280_22_60.7	-	-	-	-
WW_rs43668789_11_21.3	SOUND	3591	18,215,471 – 23,417,727	Buitenhuis et al., 2007
	RFI	5281	8,076,786 – 33,430,175	Sherman et al., 2009
	RANGLE	3447	16,291,959 – 80,096,141	Boichard et al., 2003
	WWTMM	10894	16,291,959 – 80,096,141	McClure et al., 2010
WW_rs136155567_27_27.0	BQ	3598	24,473,016–31,018,770	Buitenhuis et al., 2007
	SOUND	3594	24,473,016–31,018,770	Buitenhuis et al., 2007
	ADFI	21028	27,034,490 – 29,073,970	Rolf et al., 2012
	ADG	20979	27,034,490 – 29,073,970	Rolf et al., 2012
	RFI	21095	27,034,490 – 29,073,970	Rolf et al., 2012
	CALEASE	11259	21,801,052 – 31,012,980	McClure et al., 2010
¹ ADG= average daily gain; ADFI = average daily feed intake; BQ = bone quality; CALEASE = calving ease; RFI = residual feed intake; RANG = rump angle; SOUND = structural soundness; WWTMM = weaning weight-maternal milk. ² ID = identification.				

Table 4
Genes close to the SNP rs133262280_22 associated with birth weight of Braunvieh cattle.

SNP_BTA	Gene in ± 250 kb ¹	Gene ID ²	Distance, ³ kb	Description
rs133262280	PODXL2	532521	U 202.2	Podocalyxin like 2
	MCM2	510120	U 177.6	Minichromosome maintenance complex component 2
	TPRA1	617772	U 160.1	Transmembrane protein adipocyte associated 1
	LOC10105309	109905309	U 57.8	Uncharacterized LOC101905309
	PLXNA1	531240	D 192.2	Plexin A1
	CHCHD6	615934	D 200.9	Coiled-coil-helix-coiled-coil-helix domain containing 6
¹ rs136155567: gene in ± 600 kb ² ID = identification. ³ D = downstream; U = upstream.				

Table 5
Genes close to the SNPs associated to weaning weight of Braunvieh cattle.

SNP_BTA	Gene in \pm 250 kb ¹	Gene ID ²	Distance, ³ kb	Description
rs43668789	GALM	616676	U 217.4	Galactose mutarotase
	SRSF7	507066	U 201.6	Serine and arginine rich splicing factor 7
	GEMIN6	525263	U 160.6	Gem nuclear organelle associated protein 6
	LOC107132913	107132913	U 156.0	Uncharacterized LOC107132913
	DHX57	540993	U 86.1	Dexh-box helicase 57
	MORN2	616607	U 77.8	MORN repeat containing 2
	ARHGEF33	100335703	Cover	Rho guanine nucleotide exchange factor 33
	SOS1	537682	D 17.0	SOS Ras/Rac guanine nucleotide exchange factor 1
	MIR2284Z-2	102465308	D 62.5	Microrna 2284z-2
	LOC104973309	104973309	D 121.0	Ubiquitin-40S ribosomal protein S27a pseudogene
	CDKL4	517478	D 207.4	Cyclin dependent kinase like 4
	LOC782845	782845	D 241.7	60S ribosomal protein L23a pseudogen
rs136155567_27	LOC104976093	104976093	D 470.9	Uncharacterized LOC104976093
	NRG1	281361	D 567.1	Neuregulin 1
¹ rs136155567: gene in \pm 600 kb ² ID = identification. ³ D = downstream; U = upstream.				

Discussion

The inclusion of the population's genetic structure into the analysis model allowed the better fitting of the GWAS model for all traits, as showed by quantile-quantile plots (Fig. 1). This genetic structure was expected because tested herds presented different selection criteria, and perhaps, ancestors from the imported genetic material (*i.e.*, semen, sires). Stratification results could include extensive use of sires or semen that breeders usually choose in their genetic improvement programs. Some studies (Erbe et al., 2012; Plieschke et al., 2015) have used subdivisions to estimate QTLs using genome-wide association studies (GWAS). Smitz et al. (2014) concluded that the stratification in the studied populations needs to be considered in genetic improvement programs to conserve those populations' "genetic health". Jemaa et al. (2015) indicated that some QTLs found in GWAS could not be present in all the studied animals due to the population's stratification.

Birth weight in Braunvieh cattle represents an important trait to consider in the genetic improvement programs due to its association with calving difficulty in young heifers, especially when the Braunvieh is used as a sire for smaller-size breeds (Hagger & Hofer, 1990). In the present study, the rs133262280 was identified as the only marker associated

with BW, located at 60.7 Mb of BTA 22. This SNP showed an allelic substitution effect of 0.320 kg, explaining 0.1% of the phenotypic variance of BW. Genes located closer to this SNP included *CHCHD6* (coiled-coil-helix-coiled-coil-helix domain containing 6), *MCM2* (mini-chromosome maintenance complex component 2), *PLXNA1* (plexin A1), *PODXL2* (podocalyxin like 2), *TPRA1* (transmembrane protein adipocyte associated 1), and uncharacterized *LOC10105309* (Table 4).

The most important genes identified in this region were *MCM2* and *TPRA1*. *MCM2* gene is located at 177.6 kb and *TPRA1* at 160.1 kb; both genes are upstream of the rs133262280 SNP. *MCM2* acts as a component of the MCM2-7 complex (MCM complex) which is the putative replicative helicase essential for 'once per cell cycle' DNA replication initiation and elongation in eukaryotic cells (Todorov et al., 1994). Additionally, it plays a role in cell division and apoptosis (Gao et al., 2015). Gao et al. (2015) reported MCM2 protein expression in the cochlea of rats and guinea pigs slightly increase the apoptosis rate of the cells without any changes in proliferation or cell cycle. Recently, Khan et al. (2020) found by a transcriptomic analysis that supplementation with folic acid in perinatal Holstein cows significantly increases the expression of the MCM2 gene.

The other associated gene with biological importance was the TPRA1 gene belongs to the G protein-coupled receptor (GPCR) family. Functions related to this gene include regulating early embryonic cleavage and enhancing the hedgehog signaling pathway (Aki et al., 2008; Singh et al., 2015). Several studies have highlighted its importance in pre-and perinatal tissue development in mice. Aki et al. (2015) determined that the TPRA1 gene influenced the hedgehog signaling pathway, which plays an essential role in vertebrate embryonic tissue patterning of many developing organs, showing differences around 50% in the signaling levels comparing homozygotes and heterozygotes animals.

This evidence suggests that MCM2 and TPRA1 could participate in the early stages of cattle development and, therefore, influence BW. There were no quantitative trait loci previously located in this region, which could be a specific QTL of the studied population.

The present study identified two regions (Table 3, WW_rs43668789_11_21.3 and WW_rs136155567_27_27.0) previously reported by McClure et al. (2010) as associated with weaning weight and calving ease in Angus cattle. Besides, Boichard et al. (2003) and Buitenhuis et al. (2007) reported associations between the identified regions in this study and conformation traits, explaining between 5.9 to 8.9 % of the structural soundness in ten European dairy cattle breeds. On the other hand, Sherman et al. (2009) and Rolf et al. (2012) reported associations with allele substitution effects between - 0.319 to 2.199 kg for feeding traits like average daily gain and residual feed intake in Angus, Charolais, and Canadian beef hybrid cattle.

Two SNPs markers were associated with WW. One of these markers was rs43668789, located at 21.3 Mb of BTA 11 and showed an allelic substitution effect of -9.590 kg and explaining almost 3% of the phenotypic variance of WW. Genes located closer or covering this SNP included ARHGEF33 (Rho guanine nucleotide exchange factor 33), CDKL4 (cyclin-dependent kinase-like 4), DHX57 (DEXH-box helicase 57), GALM (galactose mutarotase), GEMIN6 (gem nuclear organelle associated protein 6), LOC104973309 (ubiquitin-40S ribosomal protein S27a pseudogene), LOC107132913 (uncharacterized LOC107132913), LOC782845 (60S ribosomal protein L23a pseudogene), MAP4K3 (mitogen-activated protein kinase 3), MIR2284Z-2 (microRNA 2284z-2), MORN2 (MORN repeat containing 2), SOS1 (SOS Ras/Rac guanine nucleotide exchange factor 1), and SRSF7 (serine and arginine-rich splicing factor 7) (Table 5).

The most important gene identified in this region was *GALM*. This gene is located 217.4 kb upstream of the rs43668789 and belongs to the proteins that convert the α -aldose to β -anomer. *GALM* is involved in the pathway hexose metabolism, which is part of carbohydrate metabolism (Thoden et al., 2004). McClure et al. (2010) reported a

positive association of *GALM* with the weaning weight in Angus cattle. Shin et al. (2014) mentioned that the association between *GALM* and the weaning weight in Holstein and Hanwoo cattle lies in quantity and the quality of the calves' milk consumption. Quantitative trait loci located in this region have been previously associated with weaning weight in Angus (McClure et al., 2010), conformation in dairy cattle breed (Boichard et al., 2003; Buitenhuis et al., 2007), and residual feed intake in Canadian beef synthetic cattle (Sherman et al., 2009).

The second marker associated with WW was rs136155567, located at 27.0 Mb of BTA 27, and its allele substitution effect was 1.110 kg which explains 1.1% of the phenotypic variance. Genes located closer to this SNP (± 600 kb) included *LOC104976093* (uncharacterized LOC104976093) and *NRG1* (neuregulin 1) (Table 5). *NRG1* was the most important gene identified. This gene is located at 567.1 kb downstream of the rs136155567. It is considered the direct ligand for ERBB3 and ERBB4 tyrosine kinase receptors. The multiple isoforms perform diverse functions such as inducing growth and differentiation of epithelial, glial, neuronal, and skeletal muscle cells and influence motor and sensory neuron development (Ieguchi et al., 2010; Plowman et al., 1993). In cattle, *NRG1* has been highly associated with organ development (Sweeney et al., 2001). Zhao (2013) mentioned that this gene could influence the weaning weight as an emerging regulator of prolactin secretion.

In general, the phenotypic variance explained by the SNPs identified by this study was marginal (1.39 % on average). In growth trait studies, it is expected that most SNP markers will explain only a tiny proportion of the observed phenotypic variance due to the polygenic control over such traits and because individual genes only slightly influence a phenotype. However, consideration of SNPs' sets that are significantly associated with each trait may allow a greater proportion of phenotypic variance to be explained. For example, the two SNP associated with WW could explain 4.08 % of the variance in that trait. However, the present outcomes increase knowledge of the genetic architecture of live weight traits important in beef cattle production.

In conclusion, in the present study, three SNP were associated with live weight traits of Braunvieh cattle. Two SNPs were located in intergenic regions, and one was located in an intronic region of the *ARHGEF33* gene. Evidence shows that some of the genes closer to the three identified SNPs markers are functionally related to growth through embryonic cleavage, bone and tissue growth, cell adhesion, and organ development. There were four candidate genes with potential associations with assessed live weight traits in Braunvieh cattle, including *MCM2*, *TPRA1*, *GALM*, and *NRG1*. Subsequent studies examining these genomic regions could lead to the identification of polymorphisms with potential uses in the marker-assisted selection, providing a deeper understanding of the genetic basis of growth traits in cattle. This study represents the first study to describe a GWAS conducted in Braunvieh cattle in Mexico. Further analysis using the present information would allow conducting assessments on the ontogeny and specific search of causative mutations for live weight traits. Furthermore, examining particular and general genic effects would indicate the possibility of including genomic information into current genetic evaluations.

Declarations

ACKNOWLEDGMENTS

Authors thank the National Council of Science and Technology (CONACYT) for supporting the first author's doctorate studies grant and to Universidad Autónoma Chapingo for the research grant DGIP-166701012. The authors also thank the Asociación Mexicana de Criadores de Ganado Suizo A. C. for their collaborative support.

Funding

This study was funded by research grant DGIP-166701012 by the Universidad Autónoma Chapingo.

Conflicts of interest/Competing interests

The authors have no conflict of interest to declare

Availability of data and material (data transparency)

Data could be available upon reasonable request to the authors.

Code availability (software application or custom code)

Code used for analysis could be available upon reasonable request to the authors.

Ethics approval

No live animals were used in this study, then was not necessary the ethics approval.

Consent to participate

Not applicable

Consent for publication

All the authors have read the content and consented to submit the manuscript

References

- Aki T, Funakoshi T, Nishida-Kitayama J and Mizukami Y (2008). TPRA40/GPR175 regulates early mouse embryogenesis through functional membrane transport by Sjögren's syndrome-associated protein NA14. *J Cell Physiol*, 217:194-206. <https://doi:10.1002/jcp.21492>
- AMCGSR (2017). Asociación Mexicana de Criadores de Ganado Suizo de Registro. *Evaluaciones genéticas*. Retrieved from <https://amcgsr.com.mx/evaluaciones-geneticas/>
- Aulchenko YS, Ripke S, Isaacs A and Van Duijn CM (2007). GenABEL: an R library for genome-wide association analysis. *Bioinformatics*, 23: 1294-1296. <https://doi:10.1093/bioinformatics/btm108>
- Jemaa BS, Boussaha M, Mehdi BM, Lee HJ and Lee SH (2015). Genome-wide insights into population structure and genetic history of tunisian local cattle using the illumina bovinesnp50 beadchip. *BMC Genomics*, 16: 677. <https://doi:10.1186/s12864-015-1638-6>
- Boichard D, Grohs C, Bourgeois F, Cerqueira F, Faugeras R, Neau A, Rupp R, Amigues Y, Boscher MY and Levéziel H (2003). Detection of genes influencing economic traits in three French dairy cattle breeds. *Gen Sel Evol* 35: 77-101. <https://doi:10.1051/gse:2002037>
- Buitenhuis AJ, Lund MS, Thomasen JR, Thomsen B, Nielsen HV, Bendixen C and Guldbandsen B (2007). Detection of quantitative trait loci affecting lameness and leg conformation traits in Danish Holstein cattle. *J Dairy Sci* 90: 472-481. [https://doi:10.3168/jds.S0022-0302\(07\)72649-8](https://doi:10.3168/jds.S0022-0302(07)72649-8)
- Chin-Colli RC, Estrada-León R, Magaña-Monforte J, Segura-Correa J and Núñez-Domínguez R (2016). Genetic parameters for growth and reproductive traits of Brown Swiss cattle from Mexico. *Eco Rec Agropec* 3:11-20.

<https://doi:10.19136/era.a3n7.167>

Elsik CG, Unni DR, Diesh CM, Tayal A, Emery ML, Nguyen HN and Hagen DE (2016). Bovine Genome Database: new tools for gleaning function from the *Bos taurus* genome. *Nucl Acids Res* 4: D834-9. <https://doi:10.1093/nar/gkv1077>

Erbe M, Hayes BJ, Matukumalli LK, Goswam S, Bowman PJ, Reich CM, Mason BA and Goddard DE (2012). Improving accuracy of genomic predictions within and between dairy cattle breeds with imputed high-density single nucleotide polymorphism panels. *J Dairy Sci* 95: 4114–4129. <https://doi:10.3168/jds.2011-5019>

Gao J, Wang Q, Dong C, Chen S, Qi Y and & Li Y (2015). Whole exome sequencing identified *mcm2* as a novel causative gene for autosomal dominant nonsyndromic deafness in a Chinese family. *PLoS ONE*, 10(7): e0133522. <https://doi:10.1371/journal>

Gondro C, Porto-Neto LR and Lee SH (2014). SNPQC—an R pipeline for quality control of Illumina SNP genotyping array data. *Anim Genet*, 45, 758-761. <https://doi:10.1111/age.12198>

Guo J, Jorjain H and Carlborg O (2012). A genome-wide association study using international breeding-evaluation data identifies major loci affecting production traits and stature in the Brown Swiss cattle breed. *BMC Genetics* 13:82. <https://doi:10.1186/1471-2156-13-82>

Hagger C and Hofer A (1990). Genetic analyses of calving traits in the Swiss Black and White, Braunvieh and Simmental breeds by REML and MAPP procedures. *Livest Prod Sci* 24:93-107. [https://doi:10.1016/0301-6226\(90\)90070-M](https://doi:10.1016/0301-6226(90)90070-M)

Hiersche M, Rühle F and Stoll M (2013). Postgwas: Advanced GWAS Interpretation in R. *PLoS ONE*, 8, e71775. <https://doi:10.1371/journal.pone.0071775>

Hu ZL, Park CA, Wu XL and Reecy JM (2013). Animal QTLdb: an improved database tool for livestock animal QTL/association data dissemination in the post-genome era. *Nucl Acids Res* 41:871-879. <https://doi:10.1093/nar/gks1150>

Ieguchi K, Fujita M, Ma Z, Davari P, Taniguchi Y, Sekiguchi K, Wang B, Takada YK, and Takada Y (2010). Direct binding of the EGF-like domain of neuregulin-1 to integrins ($\alpha\beta3$ and $\alpha6\beta4$) is involved in Neuregulin-1/ErbB signaling. *J Biol Chem* 285: 31388-31398. <https://doi:10.1074/jbc.M110.113878>

Jahuey-Martínez FJ, Parra-Bracamonte GM, Sifuentes-Rincón AM, Martínez-González JC, Gondro C, García-Pérez CA and López-Bustamante LA (2016). Genomewide association analysis of growth traits in Charolais beef cattle. *J Anim Sci* 94:4570-4582.

Khan MZ, Liu L, Zhang Z, Khan A, Wang D, Mi S, Usman T, Liu G, Guo G, Li X, Wang Y and Yu Y (2020). Folic acid supplementation regulates milk production variables, metabolic associated genes and pathways in perinatal Holsteins. *J Anim Phys Anim Nutr* 104: 483-492.

Londoño-Gil M, Flórez JCR, Lopez-Herrera A and Gonzalez-Herrera LG (2021). Genome-Wide Association Study for Growth Traits in Blanco Orejiner (Bon) Cattle from Colombia. *Livest Sci* 243: 104366. <https://doi.org/10.1016/j.livsci.2020.104366>

Lu D, Miller S, Sargolzaei M, Kelly M, Vander Voort G, Caldwell T, Wang Z, Plastow G and Moore S (2013). Genome-wide association analyses for growth and feed efficiency traits in beef cattle. *J Anim Sci* 92: 3612-3633.

<https://doi:10.2527/jas.2012-5716>

Martínez R, Bejarano D, Gómez Y, Dasoneville R, Jiménez A, Even G, Sölkner J and Mészáros G (2016). Genome-wide association study for birth, weaning and yearling weight in Colombian Brahman cattle. *Gen Mol Biol* 40: 453-459. <https://doi:10.1590/1678-4685-GMB-2016-0017>

Maxa J, Neuditschko M, Russ I, Förster M and Medugorac I (2012). Genome-wide association mapping of milk production traits in Braunvieh cattle. *J Dairy Sci* 95: 5357-5364. <https://doi:10.3168/jds.2011-4673>

McClure MC, Morsci NS, Schnabel RD, Kim JW, Yao P, Rolf MM, McKay SD, Gregg SG, Chapple RH, Northcutt SL and Taylor JF (2010). A genome scan for quantitative trait loci influencing carcass, post-natal growth and reproductive traits in commercial Angus cattle. *Anim Genet* 41, 597–607. <https://doi:10.1111/j.1365-2052.2010.02063.x>

Orantes-Zebadúa MA, Platas-Rosado D, Córdova-Avalos V, Santos-Lara MC and Córdova-Avalos A (2014). Characterization of dual purpose livestock in a Region of Chiapas, Mexico. *Eco Rec Agropec* 1:49-58. <https://doi:10.19136/era.a1n1.6>

Parra-Bracamonte GM, Sifuentes-Rincón AM, Martínez-Gonzalez JC, Magaña-Monforte JG and Jahuey-Martínez FJ (2015). Biotecnologías para el desarrollo de los sistemas pecuarios: aspectos aplicados a la ganadería bovina para carne. In R. Núñez D., R. Ramírez V., S. Fernández R., O. Araujo F., M. García W., & T. E. Díaz M. (Eds.), *La ganadería en América Latina y el Caribe: alternativas para la producción competitiva, sustentable e incluyente de alimentos de origen animal* (pp. 391-416). México: Biblioteca Básica de Agricultura.

Phillips WA, Holloway JW, Warrington B and Venuto BC (2009). Case study: Stocker and feedlot performance of beef heifers sired by Braunvieh and Wagyu Bulls from Angus, Brahman, Senepol, and Tuli-sired Damsi. *PAS* 25:809-814. [https://doi.org/10.15232/S1080-7446\(15\)30793-2](https://doi.org/10.15232/S1080-7446(15)30793-2)

Plieschke L, Edel C, Pimentel ECG, Emmerling R, Bennewitz J and Götz KU (2015). A simple method to separate base population and segregation effects in genomic relationship matrices. *Genet Sel Evol*, 47, 53. <https://doi:10.1186/s12711-015-0130-8>

Plowman GD, Green JM, Culouscou JM, Carlton GW, Rothwell VM and Buckley S (1993). Heregulin induces tyrosine phosphorylation of HER4/p180^{erbB4}. *Nature* 366: 473-475. <https://doi:10.1038/366473a0>

Price AL, Patterson NJ, Plenge RM, Weinblatt ME, Shadick NA and Reich D (2006). Principal components analysis corrects for stratification in genome-wide association studies. *Nat Genet* 38:904-909. <https://doi:10.1038/ng1847>

Purfield DC, Bradley DG, Evans RD, Kearney FJ and Berry DP (2015). Genome-wide association study for calving performance using high-density genotypes in dairy and beef cattle. *Genet Sel Evol* 47: 47. <https://doi:10.1186/s12711-015-0126-4>

Rolf MM, Taylor JF, Schnabel RD, McKay SD, McClure MC, Northcutt SL, Kerley MS and Weaber RL (2012). Genome-wide association analysis for feed efficiency in Angus cattle. *Anim Genet* 43: 367-374. <https://doi:10.1111/j.1365-2052.2011.02273.x>

Sherman EL, Nkrumah JD, Li C, Bartusiak R, Murdoch B and Moore SS (2009). Fine mapping quantitative trait loci for feed intake and feed efficiency in beef cattle. *J Anim Sci* 87: 37-45. <https://doi:10.2527/jas.2008-0876>

- Shin DH, Lee HJ, Cho S, Kim HJ, Hwang JY, Lee CK, Jeong JY, Yoon D and Kim H (2014). Deleted copy number variation of Hanwoo and Holstein using next generation sequencing at the population level. *BMC Genomics*, 15: 240. <https://doi:10.1186/1471-2164-15-240>
- Silva C, Aké R and Valle R (2002). Edad y crecimiento a la pubertad en toros Suizo Pardo en condiciones tropicales. *Cuban J Agric Sci* 36:205-210.
- Singh J, Wen X and Scales SJ (2015). The orphan G protein-coupled receptor Gpr175 (Tpra40) enhances hedgehog signaling by modulating cAMP levels. *J Biol Chem* 290: 29663-29675. <https://doi:10.1074/jbc.M115.665810>
- Smits N, Cornélis D, Chardonnet P, Caron A, Garine-Wichatitsky M, Jori F, Mouton A, Latinne A, Pigneur LM, Melletti M, Knapeckas KL, Marescaux J, Pereira CL and Michaux J (2014). Genetic structure of fragmented southern populations of African Cape buffalo (*Syncerus caffer caffer*). *BMC Evol Biol*, 14, 203. <https://doi:10.1186/s12862-014-0203-2>
- Sweeney C, Fambrough D, Huard C, Diamonti AJ, Lander ES, Cantley LC and Carraway KL (2001). growth factor-specific signaling pathway stimulation and gene expression mediated by ErbB receptors. *J Biol Chem* 275: 22685-22698. <https://doi:10.1074/jbc.M100602200>
- Takasuga A (2016). PLAG1 and NCAPG-LCORL in livestock. *Anim Sci J* 87:159-167. <https://doi:10.1111/asj.12417>
- Thoden JB, Timson DJ, Reece RJ and Holden HM (2004). molecular structure of human galactose mutarotase. *J Biol Chem* 279: 23431-23437. <https://doi:10.1074/jbc.M40234720>
- Tian D, Wang P, Tang B, Teng X, Li C, Liu X, Zou D, Song S and Zhang Z (2020). GWAS Atlas: a curated resource of genome-wide variant-trait associations in plants and animals. *Nucl Acids Res*, 48: D927-D932. <https://doi.org/10.1093/nar/gkz828>
- Todorov IT, Pepperkok R, Philipova RN, Kearsey SE, Ansorge W and Werner D (1994). A human nuclear protein with sequence homology to a family of early S phase proteins is required for entry into S phase and for cell division. *J Cell Sci* 107:253-265. <https://doi.org/10.1242/jcs.107.1.253>
- The UniProt Consortium (2017) UniProt: the universal proteinknowledgebase. *Nucl Acids Res* 49: D480-D489. <https://doi:10.1093/nar/gkaa1100>.
- Van Raden PM (2008). Efficient methods to compute genomic predictions. *J Dairy Sci* 91:4414-4423. <https://doi:10.3168/jds.2007-0980>
- Zhao W (2013). Neuregulin-1 (Nrg1): An emerging regulator of Prolactin (PRL) secretion. In Nagy G. M., & Toth B. E. (Ed.), *Prolactin* IntechOpen: United Kingdom. <https://doi:10.5772/54716>
- Zimin AV, Delcher AL, Florea L, Kelley DR, Schatz MC, Puiu D, Hanrahan F, Pertea G, Van Tassel CV, Sonstegard TS, Marçais G, Roberts M, Subramanian P, Yprke JA and Salzberg SL (2009). A whole-genome assembly of the domestic cow, *Bos taurus*. *Genome Biol* 10:R42. <https://doi:10.1186/gb-2009-10-4-r42>

Figures

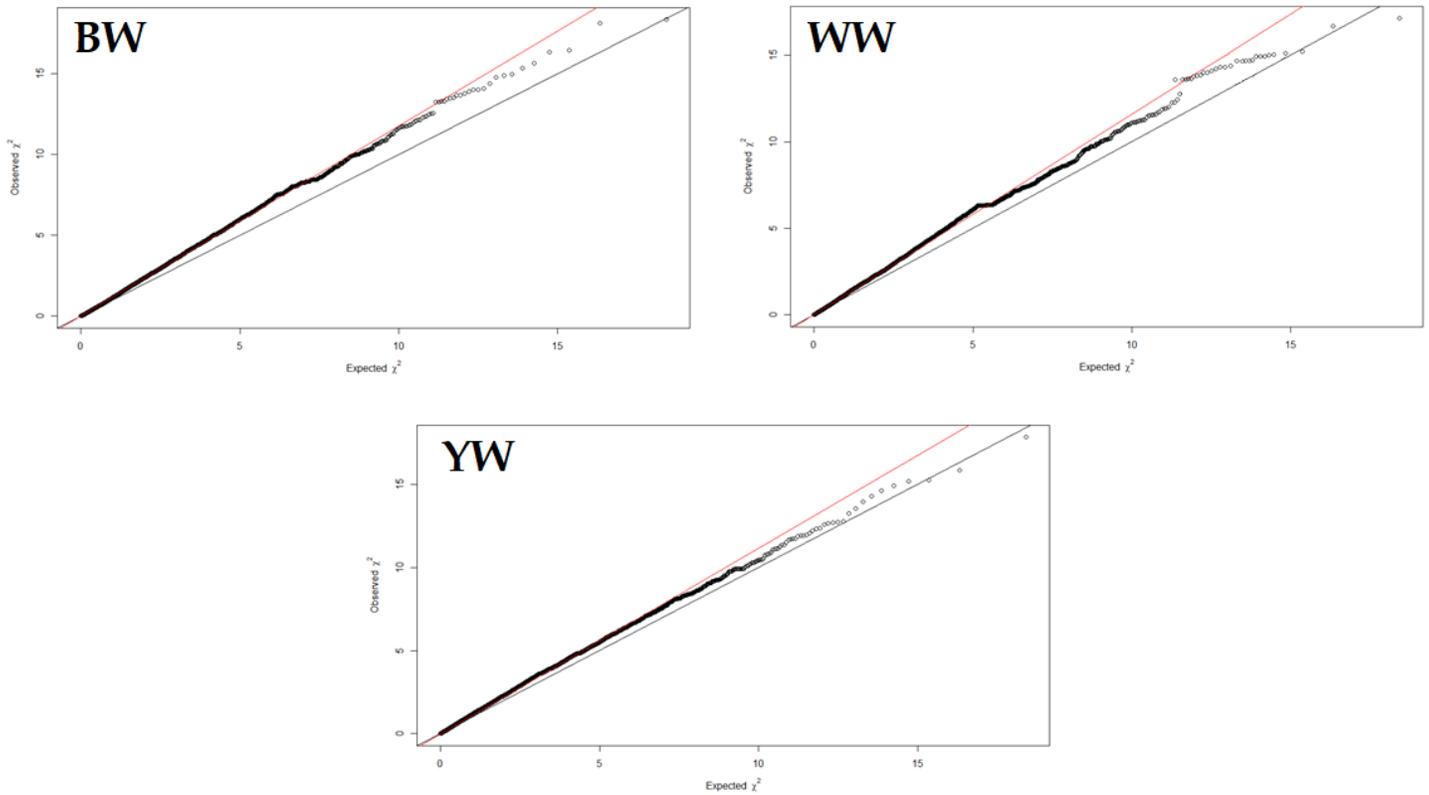


Figure 1

Quantile-quantile (QQ) plots for the genome wide association study of live weight traits in Braunvieh cattle. The straight line in the QQ plots indicates the distribution of SNP markers under the null hypothesis, and the skew at the edge indicates that these markers are more strongly associated with the traits than would be expected by chance. BW = birth weight; WW = weaning weight; YW = yearling weight.

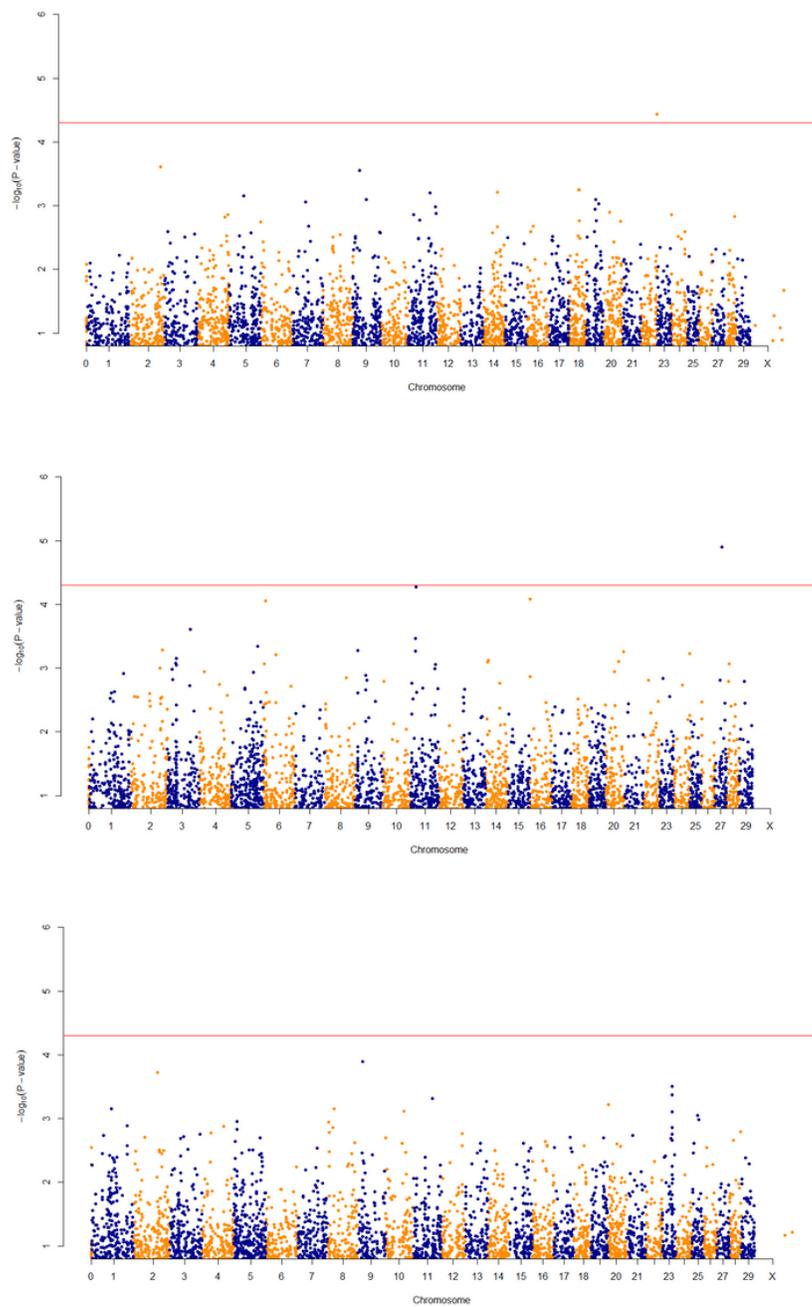


Figure 2

Manhattan plots of the P-values for the genome-wide association study of growth traits in Braunvieh cattle. The horizontal line indicates the significance threshold for significant associations ($P < 5 \times 10^{-5}$). BW = birth weight; WW = weaning weight; YW = yearling weight.