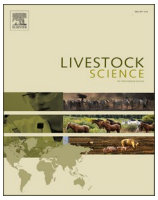
Livestock Science 264 (2022) 105048

Contents lists available at ScienceDirect

Livestock Science

journal homepage: www.elsevier.com/locate/livsci



Estimates of heritability and candidate genes for primal cuts and dressing percentage in Santa Ines sheep

Tatiana Cortez de Souza [a], Taiana Cortez de Souza [a], Valdecy Aparecida Rocha da Cruz [a], Gerson Barreto Mourão [b], Victor Breno Pedrosa [c], Gregorí Alberto Rovadoscki [b], Luiz Lehmann Coutinho [b], Gregório Miguel Ferreira de Camargo [a], Raphael Bermal Costa [a], Gleidson Giordano Pinto de Carvalho [a], Luís Fernando Batista Pinto [a,*]

[a] Federal University of Bahia, 500, Av. Adhemar de Barros, Salvador, BA 40170110, Brazil
[b] University of São Paulo, 11, Av. Pádua Dias, Piracicaba, SP 13635900, Brazil
[c] State University of Ponta Grossa, 4748, Av. General Carlos Cavalcanti, Ponta Grossa, PR 84030900, Brazil

HIGHLIGHTS

- Moderate to high estimates of heritability for primal cut yields were reported.
- Forty-three genome windows of 1.0 Mbp explained >1% of additive genetic variance.
- 355 protein-coding genes were found in the genome windows.
- Functional annotation analysis found at least 31 candidate genes for carcass traits.
- Neuroactive ligand-receptor interaction pathway was significant in functional analysis.

ARTICLE INFO

Keywords:
Carcass
GWAS
Lamb
Meat
SNPs

ABSTRACT

Primal cuts and dressing percentage are complex traits to record on a large scale, and information from molecular markers can improve the selection schemes for these traits. Thus, 490 Santa Ines lambs were genotyped for 50 K SNP chip to perform a genomic study for dressing percentage as well as shoulder, loin, rib, and leg yields. Variance components were estimated through a univariate animal model with a genomic relationship matrix. Weighted single-step association analyses were carried out to estimate the variance percentage explained by adjacent SNPs in genome windows (GW) of 1.0 Mbp. The estimates of heritability were 0.32 ± 0.14 (carcass), 0.28 ± 0.11 (loin), 0.41 ± 0.13 (rib), 0.32 ± 0.13 (shoulder), and 0.46 ± 0.13 (leg). The number of GW explaining more than 1% of additive genetic variance (VA) and the total percentages of VA explained for dressing percentage, loin, rib, shoulder, and leg yields were, respectively, eight (12.5%), ten (19.2%), nine (20.1%), ten (18.8%), and seven (13.1%). Inside the GW, 355 protein-coding genes were found, 31 of them (*FAIM, MRAS, PIK3CB, NHLH2, CASQ2, NAALADL2, ATPL1, GLIS3, TMOD1, CNTN1, LRRK2, HMGA2, MSRB3, ANKS1B, IR29A, LCORL, NCAPG, DTHD1, ARAP2, SYNE2, SPTB, KHDRBS3, CLVS1, NKAIN3, UBL3, SLC7A1, GSKIP, BDKRB2, SETD3, BCL11B* and *LRRK1*) can be considered as candidate genes for carcass traits due their biological functions. Moreover, other sixteen genes take part in the neuroactive ligand-receptor interaction pathway, and this pathway was significant in functional annotation analysis of the genes mapped for primal cuts. These results revealed novel insights regarding the genetic control for primal cuts in sheep and are a novel source of information for future genomic studies related to carcass yield in livestock.

* Corresponding author.
E-mail address: luisfbp@ufba.br (L.F.B. Pinto).

https://doi.org/10.1016/j.livsci.2022.105048
Received 17 May 2022; Received in revised form 10 August 2022; Accepted 15 August 2022
Available online 17 August 2022

1. Introduction

Higher carcass meat yield can increase the financial profitability of the sheep breeders, and primal cuts can be used as selection criteria to improve sheep meat yield. Estimates of heritability such as 0.63 (loin), 0.46 (leg), and 0.39 (shoulder) were obtained in sheep (Einarsson et al., 2015). However, these traits are measured after the slaughter, and a significant financial investment is necessary to record them. Thus, some sheep breeding programs do not use these selection criteria to improve meat yield.

Molecular marker information is used in genomic evaluation of various livestock species because it allows earlier identification of animals with better breeding values for complex traits. Moreover, the genomic data can reduce the need to perform progeny tests for carcass traits evaluation. Genome-wide association studies (GWAS) have allowed finding variants associated with carcass traits in sheep (Matika et al., 2016; Ladeira et al., 2022), but GWAS for primal cuts yields are still scarce. Thus, this study aimed to carry out GWAS analyses to identify genomic regions that explain percentages of additive genetic variance for dressing, leg, loin, shoulder, and rib percentages in Santa Ines sheep.

2. Materials and methods

2.1. Phenotypic and genotypic data

This experiment used data from five feedlots, where each feedlot had ~100 animals, totaling 490 male lambs. These animals were weaned at ~110 days old. After weaning, the lambs were exposed to a finishing period of 90 days with a diet formulation of five ingredients: corn, soybean, urea, mineral supplement, and Tifton 85 hay. The proportion of Tifton 85 hay ranged from 30% to 50%, while the urea ranged from 0.5% to 1.0%. In addition, we adjusted the proportion of both soybean and corn to allow an adequate level of both protein and energy in the diets. Although different diets have been used, all of them were formulated to allow a weight gain of 200 g day^{-1} (NRC, 2007). The animals were slaughtered at ~200 days of age, weighing an average of 38.8 kg in a single slaughterhouse, certified by the Ministry of Agriculture, Livestock and Food Supply in Brazil. Each carcass was identified and cooled in a cold chamber at −2ºC for around 24 h. Dressing percentage was calculated as a ratio between cold carcass weight and live weight at slaughter. After, the carcasses were sectioned in the middle; the left half-carcass portion was subdivided into the primal cuts as follows: shoulder (scapula, humerus, radius, and ulna region), rib (area from the first to 13th thoracic vertebra), loin (all lumbar vertebrae), and leg (the section between the last lumbar vertebra and the first sacral). Each primal cut was weighed, and its yield was calculated as a function of the cold carcass weight. Phenotype values outside ±3 standard deviations of the mean were excluded, and the descriptive statistical values for the data used in GWAS analysis can be found in Supplementary File 1.

Genotyping was performed at the Genomic Center at ESALQ/USP (Piracicaba, São Paulo, Brazil), using 54,241 SNPs from the Ovine SNP50 BeadChip (Illumina Inc., San Diego, CA). The default values of the PREGSf90 package (Misztal et al., 2014) were used for the quality control (QC) of the SNPs, which were also used by Wiggans et al. (2009). The QC consisted of excluding the SNPs: (1) located in non-autosomal chromosomes; (2) minor allele frequency (MAF) < 5%; (3) call rate < 90%; and (4) deviation from Hardy-Weinberg equilibrium (difference between observed and predicted heterozygosities > 0.15). Moreover, all 490 lambs showed a call rate > 90%. Of 54,241 SNPs, 43,996 SNPs (81.1%) passed QC and were used for the genomic analyses.

2.2. Estimates of heritability and association analysis

The variance components were estimated by the restricted maximum likelihood (REML) method, using a genomic relationship matrix in a single-trait animal model that can be described as:

$$\gamma = X\beta + Z\alpha + \varepsilon$$

where: γ is the vector of the phenotype values, X is the incidence matrix for fixed effects, β is the solution vector for the fixed effects (the contemporary group with thirty-eight levels), Z is the incidence matrix for random effects, α is the solution vector for the animal effects, and ε is the vector of the residuals. The contemporary groups were defined considering the feedlot and feed management (different diets) within each feedlot. All contemporary groups had at least six animals. A slight age difference (16 days) between the youngest and the oldest lamb was observed, and an insignificant effect ($P > 0.05$) of the covariate "age at slaughter" was found for the traits in analysis.

The genomic relationship matrix ($\boldsymbol{G}$) was created according to VanRaden (2008) as follows:

$$G = \frac{MDM'}{2\sum P_j(1-p_j)'}$$

Where $\boldsymbol{D}$ is the diagonal matrix of SNPs weights; $\boldsymbol{M}$ is a matrix of genotype centered by allele frequency (p), and $\boldsymbol{j}$ is the locus. The covariance structure for the animal effect was given by $H\sigma_a^2$, where $\boldsymbol{H}$ is a matrix that combines pedigree- and genomic-based relationships, while σ_a^2 is the additive genetic variance. The inverse of $\boldsymbol{H}$ is defined as follows:

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

Where A^{-1} is the inverse of the pedigree-based relationship matrix, A_{22}^{-1} is the inverse of the pedigree-based relationship matrix for genotyped animals, and $G^{-1}$is the inverse of the $\boldsymbol{G}$ matrix. Of the 490 genotyped lambs, 462 had phenotypes for dressing percentage, 470 had phenotypes for shoulder, loin, and leg yields, and 473 had phenotypes for rib yield.

The SNP effects were estimated using $\widehat{\mu} = qDZ'(ZDZ'q)^{-1}\widehat{a}$, where q is a weight factor based on SNPs frequency, D is a weight matrix of SNP, Z is a matrix of gene content adjusted for allele frequencies, and $\widehat{a}$ is the genomic breeding values (GEBV). In the weighted single-step GBLUP method (WssGBLUB), the genomic relationship matrix is weighted according to the proportion of additive genetic variance the SNPs explain (Misztal et al., 2014). In the first iteration, the same weight was assigned for all SNPs, while in the second iteration, the SNP weights were defined according to SNP effects ($\widehat{\mu}$) calculated in the first iteration. The percentage of additive genetic variance explained by n-adjacent SNPs in genome window (GW) of 1.0 Mbp was calculated using $\frac{Var_i}{\sigma_a^2} \times 100$, where Var_i is the variance explained by n-adjacent SNPs at i^{th} GW, and σ_a^2 is the total additive genetic variance. These percentages were used to construct Manhattan plots. All analyses, including quality control of SNPs, were performed using modules of the BLUPF90 software family (Misztal et al., 2014).

2.3. Functional annotation analyses

The traits in the present study are polygenic, and even percentages as small as 0.10% of genetic variance explained can be in regions where significant SNPs are found (Aguilar et al., 2019). Therefore, the functional annotation analyses were performed only for the genomic regions that explained the highest percentages (>1%) of genetic variance. Oar_v4.0 genome assembly on NCBI Genome Data Viewer was used to identify the genes inside GW. In the Ensembl database (https://www.ensembl.org/index.html) the biological function of the genes were identified. Functional pathway analysis was conducted on DAVID 6.8 (https://david.ncifcrf.gov/). The sheepQTLdb (https://www.animalgenome.org/cgi-bin/QTLdb/OA/index) was used to find either QTL or

associations overlapping the same segments found in the present study.

3. Results

The heritability estimates ranged from moderate to high, as follows: 0.32 ± 0.14 (dressing percentage), 0.28 ± 0.11 (loin yield), 0.41 ± 0.13 (rib yield), 0.32 ± 0.13 (shoulder yield), and 0.46 ± 0.13 (leg yield). Forty-three GW explained more than 1% of additive genetic variance (Supplementary File 2). The GW found in the present study explained 12.5% (dressing percentage), 19.2% (loin yield), 20.1% (rib yield), 18.8% (shoulder yield), and 13.1% (leg yield) of additive genetic variance (Supplementary File 2). Only one GW (OAR6_41,756,944:42,750,585) explained more than 1% of the genetic variance for two traits (loin and rib yields). The GW explaining the highest percentage of additive genetic variance of each trait are in OAR1 (dressing percentage; Fig. 1), OAR1 (rib yield; Fig. 2) OAR18 (loin yield; Fig. 2), OAR8 (Shoulder yield; Fig. 2), and OAR20 (leg yield; Fig. 2). The GW mapped in the present study overlap 182 QTLs/associations reported in the sheepQTLdb, including fifty-six specific QTLs for carcass traits (Supplementary File 3).

Inside the GW, 355 protein coding-genes were found (Supplementary File 2), and functional annotation analysis was carried out for these genes. The neuroactive ligand-receptor interaction pathway was identified as a significant pathway (P-value = 2.0E-7), and 16 protein-coding genes (*ADRB3, BDKRB1, BDKRB2, CHRNA6, CHRNB3, TAAR1, TAAR5, LOC101104757, LOC101104500, LOC101119483, LOC101102492, LOC101103241, LOC101103482, LOC101118705, LOC101118960,* and *LOC101119225*) are related to this pathway. Moreover, 31 candidate genes were found after functional annotation analysis

4. Discussion

In the present study, a relationship matrix based on pedigree and molecular information was used to estimate the heritability. Einarsson et al. (2015) estimated similar heritability (0.39 for shoulder yield and 0.46 for leg yield) using a relationship matrix based on pedigree information. Therefore, both approaches showed that primal cuts could be good selection criteria to improve carcass quality in the short or medium-term.

Despite the small sample size, our study found genomic regions that may have valuable information for sheep selection to improve carcass quality. Various GW in the present study overlap either selection signature or QTLs previously associated with carcass traits in sheep. The GWs on OAR1 (OAR1_36,252,750:37,221,480, OAR1_38,778,550:39,771,622, OAR1_92,023,325:92,893,823, and OAR1_17,955,417:18,947,659) overlap QTLs for carcass fat percentage, muscle and bone weights in the carcass, muscle depth at third lumbar, backfat at third lumbar, carcass bone percentage, and lean meat yield percentage (Cavanagh et al., 2010). Functional annotation analysis found various candidate genes in OAR1. Wang et al. (2013) reported an association of *FAIM* (Fas apoptotic inhibitory molecule) expression with slaughter weight and rump width in cattle. *MRAS* (muscle RAS oncogene homolog) encodes a member of the Ras family of small GTPases known to act in myogenesis (Suzuki et al., 2000). *PIK3CB* (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit beta) takes part in IGF-I/PI3K/Akt signaling pathway, which plays a key role in mammalian muscle development. Mice deficient in the p85 subunit of the *PIK3CB* complex showed a significant reduction in muscle weight and fiber size (Luo et al., 2006). *NHLH2* (nescient helix-loop-helix 2) has a key role as central nervous system regulator of adult body weight and a QTL for rump fat thickness in cattle was located in the region harboring the genes *NHLH2* and *CASQ2* (Weng et al., 2016). Variants in *NAALADL2* (N-acetylated alpha-linked acidic dipeptidase like 2) and *ATP1A1* (ATPase Na+/*K*+ Transporting Subunit Alpha 1) were associated with body mass index in humans (Winham et al., 2013; Christakoudi et al., 2021), while a study showed association of *ATP1A1* expression with muscle proteolysis in yak (Liu et al., 2020).

Three GW on OAR2 (OAR2_211,125,735:212,098,578, OAR2_77,695,964:78,694,120, and OAR2_123,158,012:124,128,497) also overlap QTLs for carcass trait in sheep (Cavanagh et al., 2010), while OAR2_123,158,012:124,128,497 is in a selection signature region (Saravanan et al., 2021). In OAR2, *GLIS3* (GLIS family zinc finger 3) and TMOD1 (tropomodulin 1) may be candidate genes for primal cuts. *GLIS3* positively regulates osteoblast differentiation and inhibits adipocyte differentiation, moreover variants in *GLIS3* were associated with body mass index in humans (Manning et al., 2012). *TMOD1* plays a key role in muscle physiology, and a variant in this gene was previously associated with the longissimus muscle area in pigs (Wu et al., 2009).

Three GW in OAR3 (OAR3_156,731,729:157,708,600, OAR3_164,674,856:165,607,238, and OAR3_180,605,686:181,598,247) overlap

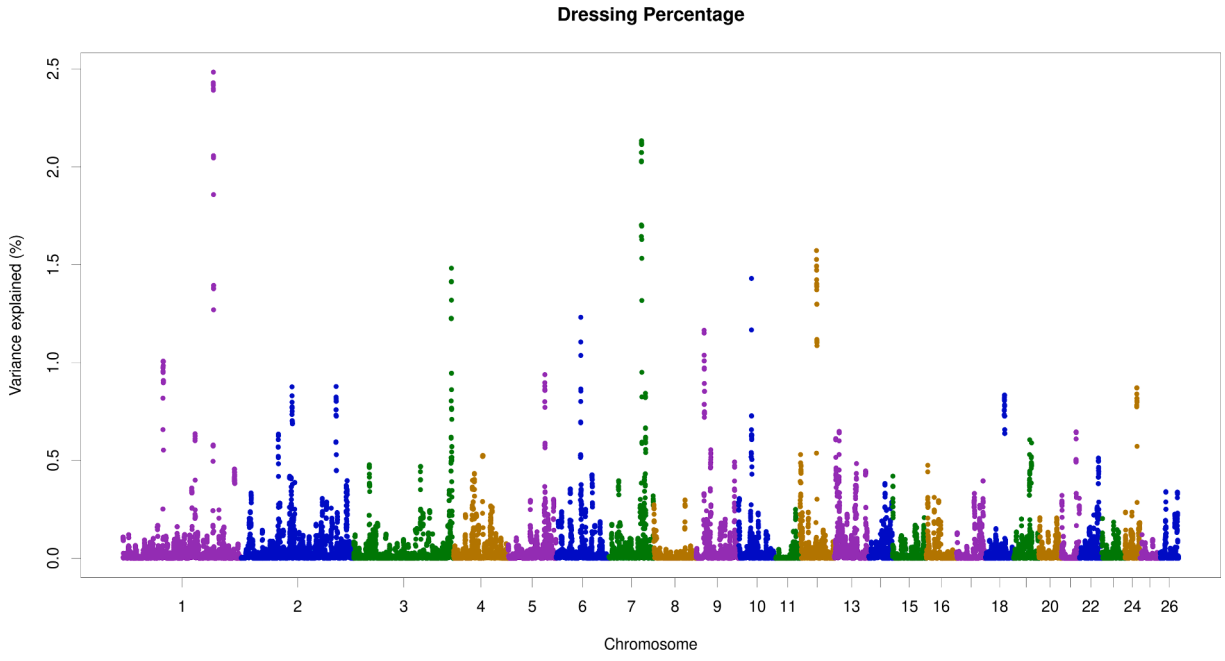


Fig. 1. Genetic variances of dressing percentage, explained by adjacent SNPs in genome windows of 1.0 Mbp in Santa Ines sheep.

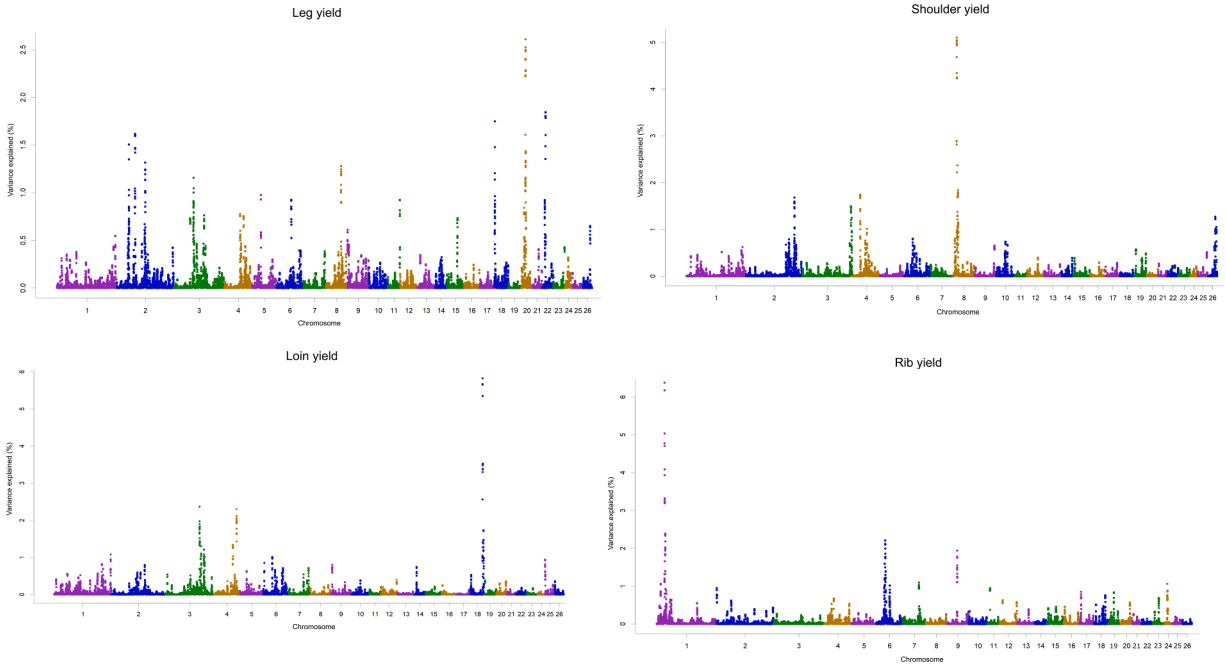


Fig. 2. Genetic variances of primal cut yields, explained by adjacent SNPs in genome windows of 1.0 Mbp in Santa Ines sheep.

selection signature region in sheep (Kijas et al., 2012; Yurchenko et al., 2019). Moreover, a copy number variation (CNV) on OAR3 was associated with carcass yield in Santa Ines sheep (Ladeira et al., 2022). Some candidate genes were found in OAR3. *CNTN1* (contactin 1) was previously associated with muscle development in mice (Davisson et al., 2011). *LRRK2* (leucine-rich repeat kinase 2) that takes part in key signaling pathways for myogenesis (Von-Maltzahn et al., 2012). *HMGA2* (high mobility group AT-hook 2) plays an essential role in preadipocyte proliferation and is located in a region harboring a QTL associated with loin eye area in cattle (Saatchi et al., 2014). *MSRB3* (methionine sulfoxide reductase B3) was associated with chest circumference, hip height, body weight, chest-length index, and huckle bone width in cattle (Wu et al., 2019). *ANKS1B* (ankyrin repeat and sterile alpha motif domain containing 1B) has been associated with body size and morphology in sheep (Zhang et al., 2013; Kominakis et al., 2017).

OAR4_102,691,147:103,688,446 is overlapping a selection signature region reported by Yurchenko et al. (2019). Inside this GW was found the gene *MIR29A* (microRNA 29a), which plays a critical role in the muscle growth of Hu sheep by reducing the expression of genes (*YAP1, MyoG, MyoD*, and *MyHC*) that are related to the proliferation and differentiation of skeletal muscle satellite cells (Wu et al., 2020).

Four GW in OAR6 (OAR6_41,756,944:42,750,585, OAR6_39,816,933:40,816,015, OAR6_37,911,182:38,882,120, OAR6_41,756,944:42,750,585) overlap QTLs for hot carcass weight, bone area, fat weight in the carcass, total bone, bone area, bone density, fat weight in carcass, total fat area, and muscle density (Cavanagh et al., 2010; Matika et al., 2016). The OAR6_41,756,944:42,750,585 also overlaps the selection signature region reported in three previous studies in sheep (Kijas et al., 2012; Rochus et al., 2018; Yurchenko et al., 2019). In OAR6, the genes *LCORL* (ligand-dependent nuclear receptor corepressor like) and *NCAPG* (non-SMC condensin I complex subunit G) were associated with both muscle and fat deposition-related traits in sheep (Matika et al., 2016; Zlobin et al., 2021). Variants in the genes *DTHD1* (death domain containing 1) and *ARAP2* (ArfGAP with RhoGAP domain, ankyrin repeat and pH domain 2) were associated with loin strength, a morphometric score trait measured in dairy cattle (Lu et al., 2021).

In OAR7 were found a GW (OAR7_73,038,785:74,033,381) that overlaps a QTL for bone density in sheep (Matika et al., 2016); while the GWs on OAR9 (OAR9_18,891,285:19,823,427 and OAR9_43,031,727:44,011,965) overlap QTLs for muscle weight in carcass, hot carcass weight, and longissimus muscle area in sheep (Cavanagh et al., 2010). Two candidate genes were found in OAR7 because previous genome-wide studies in cattle found variants in *SYNE2* (Spectrin Repeat Containing Nuclear Envelope Protein 2) and *SPTB* (Spectrin beta, erythrocytic) associated with both meat quality and carcass quality traits (Rezende et al., 2021; Leal-Gutiérrez et al., 2018). On OAR9, three candidate genes were found. *KHDRBS3* (KH RNA binding domain containing, signal transduction associated 3) may play a role as inhibitor of cell proliferation and was suggested as a candidate gene for primal cut yields in cattle (Naserkheil et al., 2021); while variants in both *CLVS1* (Clavesin 1) and *NKAIN3* (Sodium/Potassium Transporting ATPase Interacting 3) were associated with body mass index and body height in humans (Tachmazidou et al., 2017; Richardson et al., 2020).

Some candidate genes for dressing percentage may be located in OAR10 (OAR10_30,591,945:31,575,000), because this region overlaps various QTLs for carcass traits in sheep, including fat weight in carcass, carcass bone percentage, carcass fat percentage, and lean meat yield percentage (Cavanagh et al., 2010). Moreover, a previous study found SNPs, in this same region of OAR10, associated with body measurements in sheep (Posbergh *et al.*, 2021); while variants in *UBL3* (Ubiquitin Like 3) and *SLC7A1* (Solute Carrier Family 7 Member 1) were previously associated with body height in human (Tachmazidou et al., 2017).

The present study also found GWs in the telomeric region of OAR18, which is known to harbor variants and haplotypes with a significant effect on muscle development in sheep, resulting in phenotypes such as *Callipyge* and *Carwell* (Tellam et al., 2012). The OAR18_60,775,598:61,772,991 overlaps QTLs for subcutaneous fat thickness and muscle depth at the third lumbar (Walling et al., 2004). Five candidate genes were found in OAR18. *GSKIP* (GSK3B interacting protein) encodes a protein that acts in the Wnt signaling pathway, which plays a crucial role in myogenesis (Von-Maltzahn et al., 2012); while *BDKRB2* (bradykinin receptor B2) takes part in signaling pathways that may cause muscle hypertrophy in mice (Verbrugge et al., 2018). *SETD3* (SET domain containing 3, actin histidine methyltransferase) is highly expressed in muscle tissue. It activates the transcription of genes such as *MyoG* (Myogenin), *CKM* (Creatine kinase, muscle), and *MyF6* (Myogenic Factor 6), which are associated with muscle development. *BCL11B* (BAF chromatin remodeling complex subunit BCL11B) is a member of the

NF-kappaB signaling pathway, which also plays an essential role in myogenesis, influencing muscle hypertrophy (Peterson et al., 2011). *LRRK1* (leucine-rich repeat kinase 1) is involved in the trafficking of epidermal growth factor receptor (EGFR), which stimulates the growth process in various tissues (Widmann et al., 2013). Variants in *LRRK1* were associated with height (Tachmazidou et al., 2017) and body weight (Galván-Femenía et al., 2018) in humans.

Although 355 protein-coding genes have been found in the present study, only one significant pathway (neuroactive ligand-receptor interaction pathway) was observed. Of sixteen genes found in this pathway, eleven of them encode G protein-coupled trace amine-associated receptors. These receptors are involved in complex signaling pathways to stimulate protein synthesis selectively and promote skeletal muscle maturation and growth (Guttridge, 2011). Moreover, meat quality traits in beef cattle may also be associated with this pathway (Tizioto et al., 2013). Therefore, the results of the present study showed a candidate pathway that may have significant importance for sheep carcass quality.

5. Conclusion

Despite its small sample size, this study indicated a moderate to high heritability in primal cut yields in Santa Ines sheep, showing the possibility of using pedigree and genomic information in selection schemes to improve carcass quality. At least forty-three genome windows of 1.0 Mbp can explain more than 1% of additive genetic variance of primal cut yields and dressing percentage in Santa Ines sheep. Inside genome windows, at least thirty-one candidate genes deserve posterior studies to find genetic additive effects for carcass traits in sheep because these genes are involved with various biological processes, especially muscle growth. Moreover, the neuroactive ligand-receptor interaction pathway may be key to understanding the biological control of carcass-related traits in sheep.

Funding statement

This study was supported by FAPESB [PNE0006/2014]; CNPq, [455,611/2014-9]; - FAPESP [2015/25,024-5 and 13/04,504-3]; and CAPES [Code 001].

Ethics approval statement

The Ethics Committee on Animal Use of the Veterinary Medicine and Animal Science School in Federal University of Bahia (Protocol number 07/2016) previously approved this study.

CRediT authorship contribution statement

Tatiana Cortez de Souza: Formal analysis, Investigation, Writing – original draft. **Taiana Cortez de Souza:** Investigation. **Valdecy Aparecida Rocha da Cruz:** Writing – review & editing. **Gerson Barreto Mourão:** Funding acquisition. **Victor Breno Pedrosa:** Writing – review & editing. **Gregorí Alberto Rovadoscki:** Investigation. **Luiz Lehmann Coutinho:** Resources. **Gregório Miguel Ferreira de Camargo:** Writing – review & editing. **Raphael Bermal Costa:** Formal analysis. **Gleidson Giordano Pinto de Carvalho:** Investigation. **Luís Fernando Batista Pinto:** Conceptualization, Resources, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

None.

Acknowledgments

The authors thank Dr. Luiz Lehmann Coutinho for the infrastructure of the Animal Biotechnology Laboratory of ESALQ/USP. LL Coutinho, GB Mourão, RB Costa, GGP Carvalho, GMF Camargo, VB Pedrosa, and LFB Pinto are recipients of a CNPq Productivity Scholarship. VAR Cruz is a recipient of a CAPES Post-Doctoral Fellowship.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.livsci.2022.105048.

References

Aguilar, I., Legarra, A., Cardoso, F., Masuda, Y., Lourenco, D., Misztal, I., 2019. Frequentist p-values for large-scale-single step genome-wide association, with an application to birth weight in American Angus cattle. Genet. Sel. Evol. 51, 28. https://doi.org/10.1186/s12711-019-0469-3.

Cavanagh, C.R., Jonas, E., Hobbs, M., Thomson, P.C., Tammen, I., Raadsma, H.W., 2010. Mapping Quantitative Trait Loci (QTL) in sheep. III. QTL for carcass composition traits derived from CT scans and aligned with a meta-assembly for sheep and cattle carcass QTL. Genet. Sel. Evol. 42, 36. https://doi.org/10.1186/1297-9686-42-36.

Christakoudi, S., Evangelou, E., Riboli, E., Tsilidis, K.K., 2021. GWAS of allometric body-shape indices in UK Biobank identifies loci suggesting associations with morphogenesis, organogenesis, adrenal cell renewal and cancer. Sci. Rep. 11, 10688. https://doi.org/10.1038/s41598-021-89176-6.

Davisson, M.T., Bronson, R.T., Tadenev, A.L.D., Motley, W.W., Krishnaswamy, A., Seburn, K.L., Burgess, R.W., 2011. A spontaneous mutation in Contactin 1 in the Mouse. PLoS One 6, e29538. https://doi.org/10.1371/journal.pone.0029538.

Einarsson, E., Eythórsdóttir, E., Smith, C.R., Jónmundsson, J.V., 2015. Genetic parameters for lamb carcass traits assessed by video image analysis, EUROP classification and *in vivo* measurements. Icel. Agric. Sci. 28, 3–14. https://doi.org/10.16886/IAS.2015.01.

Galván-Femenía, I., Obón-Santacana, M., Piñeyro, D., Guindo-Martinez, M., Duran, X., Carreras, A., Pluvinet, R., Velasco, J., Ramos, L., Aussó, S., Mercader, J.M., Puig, L., Perucho, M., Torrents, D., Moreno, V., Sumoy, L., de Cid, R., 2018. Multitrait genome association analysis identifies new susceptibility genes for human anthropometric variation in the GCAT cohort. J. Med. Genet. 55, 765–778. https://doi.org/10.1136/jmedgenet-2018-105437.

Guttridge, D.C., 2011. Making muscles grow by g protein-coupled receptor signaling. Sci. Signal. 4, pe45. https://doi.org/10.1126/scisignal.2002670.

Kijas, J.W., Lenstra, J.A., Hayes, B., Boitard, S., Porto-Neto, L.R., San-Cristobal, M., Servin, B., McCulloch, R., Whan, V., Gietzen, K., Paiva, S., Barendse, W., Ciani, E., Raadsma, H., McEwan, J., Dalrymple, B., International Sheep Genomics Consortium Members, 2012. Genome-wide analysis of the world's sheep breeds reveals high levels of historic mixture and strong recent selection. PLoS Biol. 10, e1001258 https://doi.org/10.1371/journal.pbio.1001258.

Kominakis, A., Hager-Theodorides, A.L., Zoidis, E., Saridaki, A., Antonakos, G., Tsiamis, G., 2017. Combined GWAS and 'guilt by association'-based prioritization analysis identifies functional candidate genes for body size in sheep. Genet. Sel. Evol. 49, 41. https://doi.org/10.1186/s12711-017-0316-3.

Ladeira, G.C., Pilonetto, F., Fernandes, A.C., Bóscollo, P.P., Dauria, B.D., Titto, C.G., Coutinho, L.L., Silva, F.F., Pinto, L.F.B., Mourão, G.B., 2022. CNV detection and their association with growth, efficiency, and carcass traits in Santa Inês sheep. J. Anim. Breed. Genet. https://doi.org/10.1111/jbg.12671. Advance online publication.

Leal-Gutiérrez, J.D., Rezende, F.M., Elzo, M.A., Johnson, D., Peñagaricano, F., Mateescu, R.G., 2018. Structural equation modeling and whole-genome scans uncover chromosome regions and enriched pathways for carcass and meat quality in beef. Front. Genet. 9, 532. https://doi.org/10.3389/fgene.2018.00532.

Liu, Y.X., Ma, X.M., Xiong, L., Wu, X.Y., Liang, C.N., Bao, P.J., Yu, Q.L., Yan, P., 2021. Effects of intensive fattening with total mixed rations on carcass characteristics, meat quality, and meat chemical composition of yak and mechanism based on serum and transcriptomic profiles. Front. Vet. Sci. 21, 599418. https://doir.org/10.3389/fvets.2020.599418.

Lu, X., Abdalla, I.M., Nazar, M., Fan, Y., Zhang, Z., Wu, X., Xu, T., Yang, Z., 2021. Genome-Wide Association study on reproduction-related body-shape traits of chinese holstein cows. Animals 11 (7), 1927. https://doi.org/10.3390/ani11071927.

Luo, J., Sobkiw, C.L., Hirshman, M.F., Logsdon, M.N., Li, T.Q., Goodyear, L.J., Cantley, L. C., 2006. Loss of class IA PI3K signaling in muscle leads to impaired muscle growth, insulin response, and hyperlipidemia. Cell Metab. 3, 355–366. https://doi.org/10.1016/j.cmet.2006.04.003.

Manning, A.K., Hivert, M.F., Scott, R.A., Grimsby, J.L., Bouatia-Naji, N., Chen, H., Rybin, D., Liu, C.T., Bielak, L.F., Prokopenko, I., Amin, N., Barnes, D., Cadby, G., Hottenga, J.J., Ingelsson, E., Jackson, A.U., Johnson, T., Kanoni, S., Ladenvall, C., Lagou, V., Langenberg, C., 2012. A genome-wide approach accounting for body mass index identifies genetic variants influencing fasting glycemic traits and insulin resistance. Nat. Genet. 44, 659–669. https://doi.org/10.1038/ng.2274.

Matika, O., Riggio, V., Anselme-Molzan, M., Law, A.S., Pong-Wong, R., Archibald, A.L., Bishop, S.C., 2016. Genome-wide association reveals QTL for growth, bone and *in vivo* carcass traits as assessed by computed tomography in Scottish Blackface Lambs. Genet. Sel. Evol. 48, 11. https://doi.org/10.1186/s12711-016-0191-3.

Misztal, I., Tsuruta, S., Lourenco, D., Aguilar, I., Legarra, A., Vitezica, Z., 2014. Manual For BLUPF90 Family of Programs. University of Georgia, Athens, p. 125. Retrieved from. http://nce.ads.uga.edu/wiki/lib/exe/fetch.php?media=blupf90_all2.pdf. Accessed July 2, 2021.

Naserkheil, M., Mehrban, H., Lee, D., Park, M.N., 2021. Genome-wide association study for carcass primal cut yields using single-step bayesian approach in Hanwoo Cattle. Front. Genet. 12, 752424 https://doi.org/10.3389/fgene.2021.752424.

NRC, 2007. National Research Council. Nutrient Requirements of Small Ruminants. Sheep, Goats, Cervids and New World Camelids. The National Academy Press, Washington, D.C.

Peterson, J.M., Bakkar, N., Guttridge, D.C., 2011. NF-κB signaling in skeletal muscle health and disease. Curr. Top. Dev. Biol. 96, 85–119. https://doi.org/10.1016/B978-0-12-385940-2.00004-8.

Posbergh, C.J., Huson, H.J., 2021. All sheeps and sizes: a genetic investigation of mature body size across sheep breeds reveals a polygenic nature. Anim. Genet. 52, 99–107. https://doi.org/10.1111/age.13016.

Rezende, F.M., Rodriguez, E., Leal-Gutiérrez, J.D., Elzo, M.A., Johnson, D.D., Carr, C., Mateescu, R.G., 2021. Genomic approaches reveal pleiotropic effects in crossbred beef cattle. Front. Genet. 12, 627055 https://doi.org/10.3389/fgene.2021.627055.

Richardson, T.G., Sanderson, E., Elsworth, B., Tilling, K., Davey Smith, G., 2020. Use of genetic variation to separate the effects of early and later life adiposity on disease risk: mendelian randomisation study. BMJ 369. https://doi.org/10.1136/bmj.m1203. ***m1203***.

Rochus, C.M., Tortereau, F., Plisson-Petit, F., Restoux, G., Moreno-Romieux, C., Tosser-Klopp, G., Servin, B., 2018. Revealing the selection history of adaptive loci using genome-wide scans for selection: an example from domestic sheep. BMC Genom. 19, 71. https://doi.org/10.1186/s12864-018-4447-x.

Saatchi, M., Schnabel, R.D., Taylor, J.F., Garrick, D.J., 2014. Large-effect pleiotropic or closely linked QTL segregate within and across ten US cattle breeds. BMC Genom. 15, 442. https://doi.org/10.1186/1471-2164-15-442.

Saravanan, K.A., Panigrahi, M., Kumar, H., Bhushan, B., Dutt, T., Mishra, B.P., 2021. Genome-wide analysis of genetic diversity and selection signatures in three Indian sheep breeds. Livest. Sci. 243, 104367 https://doi.org/10.1016/j.livsci.2020.104367.

Suzuki, J., Kaziro, Y., Koide, H., 2000. ositive regulation of skeletal myogenesis by R-Ras. Oncogene 19, 1138–1146. https://doi.org/10.1038/sj.onc.1203402.

Tachmazidou, I., Süveges, D., Min, J.L., Ritchie, G., Steinberg, J., Walter, K., Iotchkova, V., Schwartzentruber, J., Huang, J., Memari, Y., McCarthy, S., Crawford, A.A., Bombieri, C., Cocca, M., Farmaki, A.E., Gaunt, T.R., Jousilahti, P., Kooijman, M.N., Lehne, B., Malerba, G., Zeggini, E., 2017. Whole-genome sequencing coupled to imputation discovers genetic signals for anthropometric traits. Am. J. Hum. Genet. 100, 865–884. https://doi.org/10.1016/j.ajhg.2017.04.014.

Tellam, R.L., Cockett, N.E., Vuocolo, T., Bidwell, C.A., 2012. Genes contributing to genetic variation of muscling in sheep. Front. Genet. 3, 164. https://doi.org/10.3389/fgene.2012.00164.

Tizioto, P.C., Decker, J.E., Taylor, J.F., Schnabel, R.D., Mudadu, M.A., Silva, F.L., Mourão, G.B., Coutinho, L.L., Tholon, P., Sonstegard, T.S., Rosa, A.N., Alencar, M.M., Tullio, R.R., Medeiros, S.R., Nassu, R.T., Feijó, G.L., Silva, L.O., Torres, R.A., Siqueira, F., Higa, R.H., Regitano, L.C., 2013. Genome scan for meat quality traits in Nelore beef cattle. Physiol. Genom. 45, 1012–1020. https://doi.org/10.1152/physiolgenomics.00066.2013.

VanRaden, P.M., 2008. Efficient methods to compute genomic predictions. J. Dairy Sci. 91, 4414–4423. https://doi.org/10.3168/jds.2007-0980.

Verbrugge, S., Schönfelder, M., Becker, L., Yaghoob-Nezhad, F., Hrabě de Angelis, M., Wackerhage, H., 2018. Genes whose gain or loss-of-function increases skeletal muscle mass in Mice: a systematic literature review. Front. Physiol. 9, 553. https://doi.org/10.3389/fphys.2018.00553.

Von-Maltzahn, J., Chang, N.C., Bentzinger, C.F., Rudnicki, M.A., 2012. Wnt signaling in myogenesis. Trends Cell Biol. 22, 602–609. https://doi.org/10.1016/j.tcb.2012.07.008.

Walling, G.A., Visscher, P.M., Wilson, A.D., McTeir, B.L., Simm, G., Bishop, S.C., 2004. Mapping of quantitative trait loci for growth and carcass traits in commercial sheep populations. J. Anim. Sci. 82, 2234–2245. https://doi.org/10.2527/2004.8282234x.

Wang, L.J., Liu, X.L., Wang, H.L., He, H., Li, Z.X., Chen, L., 2013. Expression analysis, single nucleotide polymorphisms and combined genotypes in candidate genes and their associations with growth and carcass traits in Qinchuan cattle. Mol. Biol. Rep. 40, 2335–2346. https://doi.org/10.1007/s11033-012-2315-3.

Weng, Z., Su, H., Saatchi, M., Lee, J., Thomas, M.G., Dunkelberger, J.R., Garrick, D.J., 2016. Genome-wide association study of growth and body composition traits in Brangus beef cattle. Livest. Sci. 183, 4–11. https://doi.org/10.1016/j.livsci.2015.11.011.

Widmann, P., Reverter, A., Fortes, M.R., Weikard, R., Suhre, K., Hammon, H., Albrecht, E., Kuehn, C., 2013. A systems biology approach using metabolomic data reveals genes and pathways interacting to modulate divergent growth in cattle. BMC Genom. 14, 798. https://doi.org/10.1186/1471-2164-14-798.

Wiggans, G.R., Sonstegard, T.S., VanRaden, P.M., Matukumalli, L.K., Schnabel, R.D., Taylor, J.F., Schenkel, F.S., Van Tassell, C.P., 2009. Selection of single-nucleotide polymorphisms and quality of genotypes used in genomic evaluation of dairy cattle in the United States and Canada. J. Dairy Sci. 92, 3431–3436. https://doi.org/10.3168/jds.2008-1758.

Winham, S.J., Cuellar-Barboza, A.B., Oliveros, A., McElroy, S.L., Crow, S., Colby, C., Choi, D.S., Chauhan, M., Frye, M., Biernacka, J.M., 2014. Genome-wide association study of bipolar disorder accounting for effect of body mass index identifies a new risk allele in TCF7L2. Mol. Psychiatry 19, 1010–1016. https://doi.org/10.1038/mp.2013.159.

Wu, H., Zhao, S., Liu, B., Yu, M., Zhu, M., Li, C., Fan, B., 2009. Tropomodulin 1 (TMOD1) is associated with lean meat growth and meat quality in the pig. Arch. Anim. Breed. 52, 108–110. https://doi.org/10.5194/aab-52-108-2009.

Wu, M., Li, S., Zhang, G., Fan, Y., Gao, Y., Huang, Y., Lan, X., Lei, C., Ma, Y., Dang, R., 2019. Exploring insertions and deletions (indels) of MSRB3 gene and their association with growth traits in four Chinese indigenous cattle breeds. Arch. Anim. Breed. 62, 465–475. https://doi.org/10.5194/aab-62-465-2019.

Wu, T., Wang, S., Wang, L., Zhang, W., Chen, W., Lv, X., Li, Y., Hussain, Z., Sun, W., 2020. Long noncoding RNA (lncRNA) CTTN-IT1 elevates skeletal muscle satellite cell proliferation and differentiation by acting as ceRNA for YAP1 through absorbing miR-29a in Hu Sheep. Front. Genet. 11, 843. https://doi.org/10.3389/fgene.2020.00843.

Yurchenko, A.A., Deniskova, T.E., Yudin, N.S., Dotsev, A.V., Khamiruev, T.N., Selionova, M.I., Egorov, S.V., Reyer, H., Wimmers, K., Brem, G., Zinovieva, N.A., Larkin, D.M., 2019. High-density genotyping reveals signatures of selection related to acclimation and economically important traits in 15 local sheep breeds from Russia. BMC Genom. 20, 294. https://doi.org/10.1186/s12864-019-5537-0.

Zhang, L., Liu, J., Zhao, F., Ren, H., Xu, L., Lu, J., Zhang, S., Zhang, X., Wei, C., Lu, G., Zheng, Y., Du, L., 2013. Genome-wide association studies for growth and meat production traits in sheep. PLoS One 8, e66569. https://doi.org/10.1371/journal.pone.0066569.

Zlobin, A.S., Nikulin, P.S., Volkova, N.A., Zinovieva, N.A., Iolchiev, B.S., Bagirov, V.A., Borodin, P.M., Aksenovich, T.I., Tsepilov, Y.A., 2021. Multivariate analysis identifies eight novel loci associated with meat productivity traits in sheep. Gene 12, 367. https://doi.org/10.3390/genes12030367.