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Meta-analysis and systematic review of genetic parameter estimates and candidate genes for growth traits in sheep

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ABSTRACT - The objective of this study was to unravel the genetic architecture of growth traits in sheep through a meta-analysis of genetic parameters (i.e., direct, maternal, and total heritability estimates, as well as genetic correlations), a systematic review, and a functional analysis to identify candidate genes and metabolic pathways related to growth traits. A random effects model was used to obtain the pooled effect estimates for the genetic parameters, and heterogeneity was assessed using both I2 and Cochran's Q statistics. For the systematic review, genomic regions were searched in the selected scientific papers, and genes were identified using the Biomart tool. After quality control, 118 articles comprising nine traits, 504 heritability estimates, and 74 genetic correlation estimates were used for the meta-analysis, and 14 articles remained for the systematic review of the genomic regions. The pooled direct heritability estimates across studies ranged from 0.07 (±0.04) for weaning weight to 0.29 (±0.03) for weight at nine months. The systematic review identified 461 genes in the significant genomic regions. These genes were distributed across all chromosomes, with most of them located on OAR11. Some regions on chromosomes 6, 15, and 21 exhibited pleiotropic effects across traits. Pathways were mainly associated with developmental and lipid metabolic processes. Growth traits in sheep are complex, have low to moderate heritabilities, and are influenced by several genes of small effect, some of which of pleiotropic effect.

Keywords: genetic correlation, GWAS, heritability, pleiotropic, pooled estimates, weight

1. Introduction

Genetic parameter estimates are essential to accurately estimate breeding values for economically important traits and to define optimal strategies of genetic selection in a population. Due to their importance in a breeding program, several studies have estimated genetic parameters for growth traits in meat sheep (Areb et al., 2021; Bangar et al., 2021; Alemayehu et al., 2022). However, the genetic trend estimated for the growth traits reported by these studies vary widely. Recently, a few meta-analysis studies have been performed to estimate the genetic parameters for growth traits in sheep (e.g., Medrado-et al., 2021; Ambike et al., 2022); nevertheless, these studies have not investigated the genes

or genomic regions controlling these traits. Both information (i.e., genetic parameters and candidate genes) are crucial to better understand the genetic architecture controlling growth traits.

With the advent of genomic selection (Meuwissen et al., 2001), several candidate genes related to economically important traits in sheep have been uncovered through Genome-Wide Association Studies (GWAS; Kaseja et al., 2023; Lakhssassi et al., 2023; Liu et al., 2023). In this context, although GWAS have been efficient in elucidating the main biological mechanisms and identifying candidate genes associated with the traits, the usually limited sample sizes and medium-density SNP panels used in sheep studies have compromised the identification of all genetic variants (Tam et al., 2019). Additionally, due to the large genetic variety observed among sheep populations (Stachowicz et al., 2018; Oliveira et al., 2020), SNP markers usually exhibit smaller linkage disequilibrium with the QTL compared with other species (e.g., Holstein cattle; Roos et al., 2008), which may compromise the performance of the association analysis. To address these challenges, some researchers suggest comparing GWAS across different ethnic backgrounds through meta-analysis studies (Tam et al., 2019). Systematic review of GWAS results and functional analysis have been performed for several human diseases (e.g., Cardoso et al., 2020; Alsheikh et al., 2022), tick resistance in bovine (Santos et al., 2022), and litter size in pigs (Martins et al., 2022). However, to the best of our knowledge, this has not yet been performed for sheep. Using systematic review of GWAS results and functional analysis in sheep populations could help understand the genetic architecture of growth traits across different sheep breeds.

The objectives of this study were to perform a meta-analysis of genetic parameters (i.e., direct, maternal, and total heritability estimates, as well as genetic correlations) for growth traits in sheep and perform a systematic review and functional analysis to identify candidate genes and metabolic pathways associated with the mentioned traits. To address these challenges, some researchers proposed performing meta-analysis studies to compare GWAS results across various ethnic groups (Tam et al., 2019).

2. Material and methods

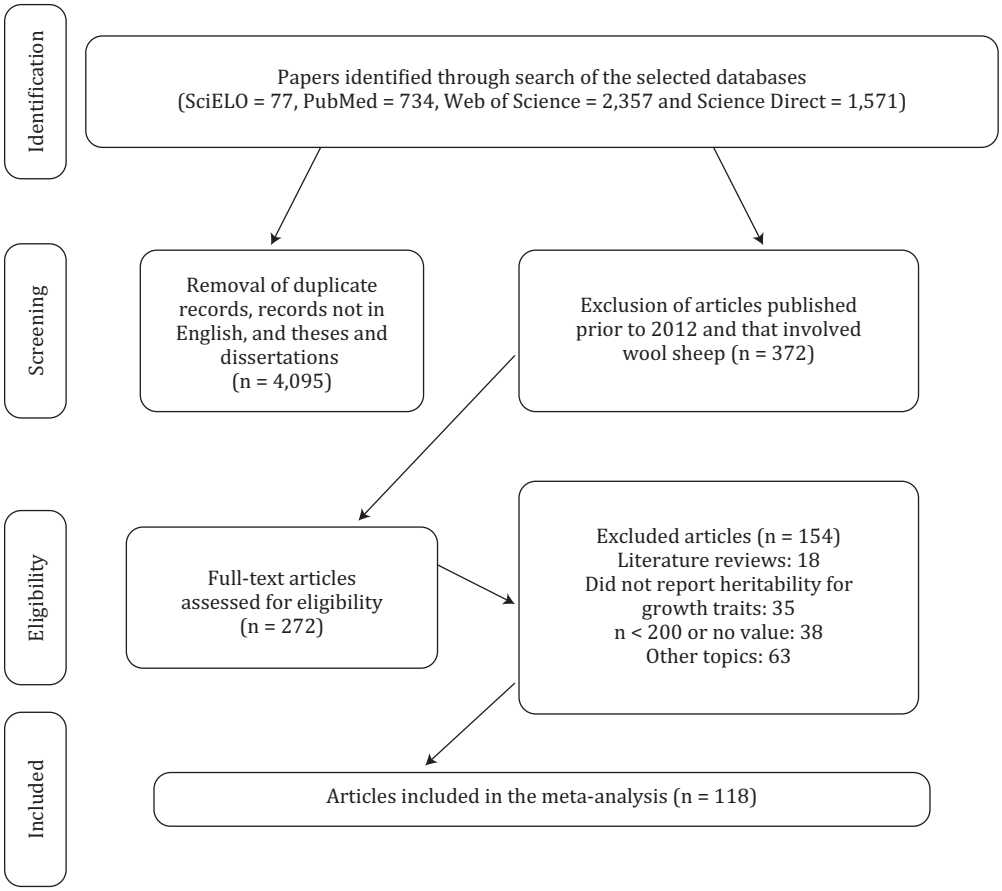
2.1. Meta-analysis of genetic parameters

2.1.1. Literature search, database, and quality control

Meta-analysis was performed according to PRISMA guidelines described in Moher et al. (2009). Articles published in indexed journals that included estimation of heritabilities and genetic correlations between weight gain and growth traits in sheep were selected. Therefore, this study comprised articles published over the last 10 years (2012-2022) in the SciELO, Web of Science, PubMed, and Science Direct electronic databases. Two authors (L. A. E. and S. S. R.) independently performed the searches between May and July 2022 using 10 combinations of keywords: (heritability) AND (sheep) NOT (milk) AND (weight gain)/(Kleiber ratio)/(birth weight)/(weaning weight)/(slaughter weight), and (genetic correlation) AND (sheep) NOT (milk) AND (weight gain)/(Kleiber ratio)/(birth weight)/(weaning weight) and (slaughter weight).

A database containing the following information of the scientific papers was created in an electronic spreadsheet: author, year of publication, journal name, volume, number of animals, statistical method used for the estimation of genetic components (i.e., REML or Bayesian), type of analysis (i.e., univariate, bivariate, or multivariate), direct heritability, maternal heritability, total heritability, genetic correlations, breed, fitness, and rearing system. Nine traits were initially recorded: body weight measured at birth, weaning, and at six, nine, and twelve months of age, average daily gain (ADG) from 0-3 and 6-9 months, and Kleiber ratio (KR) calculated from 0-3 (ADG1, KR1), 3-6 (ADG2, KR2), and 3-12 months of age (ADG3, KR3). The KR was defined as the ADG divided by the metabolic body weight (Kleiber, 1947).

The scientific papers used for the meta-analysis were selected according to the following criteria: articles addressing weight gain and growth traits in sheep, original articles, articles with n ≥ 200, and articles estimating heritabilities and genetic correlations. Duplicate articles, articles published before 2012, and articles that did not meet the selection criteria were excluded from the database. Only articles published in English were selected (Figure 1). After quality control, 118 articles remained for the meta-analysis (Supplementary material S1).



Adapted from PRISMA (Moher et al., 2009).

Figure 1 - Flow diagram of the article selection process.

2.1.2. Statistical analysis

The relative standard error (RSE) values calculated for all traits are shown in the Supplementary material S2. For papers in which the standard error of heritabilities and correlations was not reported, an approximate standard error was calculated using the combined-variance method (Sutton et al., 2000), i..e.: $SE_{ij} = \sqrt{\left(\sum_{k=1}^{K} s_{ik}^2 n_{ik}^2 / \sum_{k=1}^{K} n_{ik}\right)/n'_{ij}}$, in which SE_{ij} is the known standard error of the genetic parameter estimate for trait i in article j that did not report the standard error, s_{ik}^2 is the known standard error of the genetic parameter estimate for trait i in article k that reported the standard error, n_{ik}^2 is the number of records used to predict the parameter estimates published for trait i in article k that reported the standard error, and n'_{ij} is the number of records used to predict the parameter estimates published for trait i in article j that did not report the standard error.

For meta-analysis of genetic correlations, Fisher's *Z* transformation was performed to make them follow a normal distribution. The Z statistic was calculated as $z = 0.5log_e\left(\frac{1+r}{1-r}\right)$, in which log_e is the natural logarithm applied to logarithmic transformation when estimating the pooled effect sizes of correlation *r* across studies. Thereafter, the following equation was used to return the values to their original scale (Borenstein et al., 2009): $r^*_{gij} = \frac{e^{2Z_{ij}} - 1}{e^{2Z_{ij}} + 1}$, in which r^*_{gij} is the genetic correlation reconverted to the original scale for trait *i* in article *j*, and Z_{ij} is Fisher's *Z* statistic calculated in the previous step.

Box plots were created and weighted by the number of records to identify potential outliers using the survey package available in R (Lumley, 2020). To ensure reliability of the meta-analysis, a minimum number of articles required for each trait was obtained using the following relative standard error (RSE; Zarkovich, 1979): $RSE_i = \frac{s_i/\sqrt{n_i}}{\bar{x}_i} \times 100$, in which RSE_i is the relative standard error, given in percentage, s_i is the standard error estimated from the parameter estimates published for trait *i*, n_i is the number of articles that reported parameter estimates for trait *i*, and $\bar{x}_i$ is the mean parameter estimated for trait *i*. Traits with RSE higher than 25% were eliminated since these values indicate either few estimates for a given trait or estimates that are very discordant from the literature (Oliveira et al., 2017; Medrado et al., 2021).

After the estimation of RSE, the following parameters were discarded because of RSE < 25%: genetic correlation between weight at weaning and at six months; maternal heritability at nine and 12 months; heritability of ADG from 0-6, 3-6, 3-9, and 6-12 months; heritability of KR from 9-12 and 6-9 months; and genetic correlations between ADG from birth to weaning, weight at six months, and ADG from 6-9 months, weight at 12 months, and ADG from 9-12 months; KR from 0-6 months and weight at six months, KR from 9-12 months and weight at 12 months, and KR from 3-12 months and weight at 12 months. The following traits remained for the meta-analysis: birth weight, weaning weight, weight at six months of age, weight at nine months of age, weight at 12 months of age, ADG from birth to three months of age, KR from birth to three months, KR from birth to six months, and KR from three to six months.

As significant differences between-study heterogeneity is expected for all traits evaluated (e.g., Medrado et al. (2021)); a random effects model was used in the meta-analysis: $\widehat{\theta_k} = \theta_k + \varepsilon_k$, in which $\widehat{\theta_k}$ is the estimator of the true effect size θ_k for the *k*-th study, measured as the overall mean, and ε_k is the sampling error. The θ_k was obtained as $\theta_k = \mu + \zeta_k$, in which ζ_k is the second source of errors in addition to ε_k, which is introduced because the true effect θ_k of the *k*-th study is only part of the distribution of true effects with mean μ.

Effect sizes may vary across studies due to the effect of between-study heterogeneity (ζ_k), which can explain part of the variation observed in random-effects models. Quantifying between-study heterogeneity is important because it permits to determine how much of the variation observed between studies is due to sampling errors and how much is due to differences in true effect sizes. Several statistics can be used to calculate between-study heterogeneity (e.g., Cochran's Q, I^2, τ^2, and H^2 statistics; Harrer et al., 2021). In this study, the I^2 statistic (Higgins and Thompson, 2002) was used. The I^2 statistic was obtained as: $I^2 = \frac{Q - (K-1)}{Q}$, in which $K - 1$ is the degrees of freedom, *K* is the number of studies, and *Q* is Cochran's Q. Cochran's Q statistic (Cochran, 1954) is calculated as follows: $Q = \sum_{k=1}^{K} w_k(\widehat{\theta_k} - \hat{\theta})^2$, in which $\widehat{\theta_k}$ and $\hat{\theta}$ are as described above and w_k is the weight (importance) of each study, which is obtained as the inverse of the variance of the respective study. The smaller the variance, the higher the accuracy and, consequently, the greater the weight of the study. The w_k was obtained as $w_k = \frac{1}{s_k^2 + \tau^2}$, in which τ^2 corresponds to the variance of true effect sizes.

For each trait, the lower and upper limits of the 95% confidence interval were calculated for the estimated parameters as follows: $LL_{\bar{\theta}} = \bar{\theta} - 1.96 \times SE_{\bar{\theta}}$ and $UL_{\bar{\theta}} = \bar{\theta} + 1.96 \times SE_{\bar{\theta}}$, in which $SE_{\bar{\theta}}$ is the standard error predicted for parameter $\bar{\theta}$ described above, calculated as: $SE_{\bar{\theta}} = \sqrt{\frac{1}{\sum_{j=1}^{J} w_j}}$, in which w_j is the parameter estimate weight (assumed as the inverse of the published sampling variance for the parameter, i.e., $\frac{1}{s_j^2}$).

2.1.3. Impact of secondary variables on between-study heterogeneity

Meta-regression was performed using possible sources of between-study heterogeneity as (co)variates (i.e., breed, location of the experiment, statistical method used to predict the genetic parameters, and year of data collection). These (co)variates were organized as follows: year of data collection (1960-2019) was divided into three years [year 1 (1960 to 1980), year 2 (1981 to 2000), and year 3 (2001 to 2022)]; continent (America, Europe, Africa, Asia, and Oceania); statistical method (REML and Bayesian); breed (purebred and crossbred); type of analysis (univariate, bivariate, or multivariate); and latitude (between tropics or outside tropics). The following regression model was used: $\widehat{\theta_k} = \theta + \beta_{xk} + \varepsilon_k + \zeta_k$, in which β_{xk} is the regression coefficient. The fixed component of the model and the other variables were already described above.

The *metafor* package (Viechtbauer, 2010) of the R software was used for obtaining the meta-analysis estimates and confidence intervals using the meta-regression. Publication bias was quantified using Egger's test and visual inspection of funnel charts.

2.2. Systematic review and functional analysis of candidate genes and metabolic pathways

The search for GWAS involving growth traits in sheep was performed from October 2023 to November 2023. Only scientific papers published between 2012 and 2023 were considered. The SciELO, Web of Science, PubMed, and Science Direct electronic databases were used for the search, which used the following combination of keywords: (GWAS) AND (sheep) AND/OR (growth). The following information was retrieved from the scientific papers identified: author, year of publication, journal's name, breed, country, number of animals, trait, gene, chromosome, and start and end position. All traits related to growth in sheep (e.g., body weight, length, and height (evaluated in all ages), body condition score, average daily gain, growth rate, residual feed intake, and feed conversion) were considered for the systematic review and functional analysis.

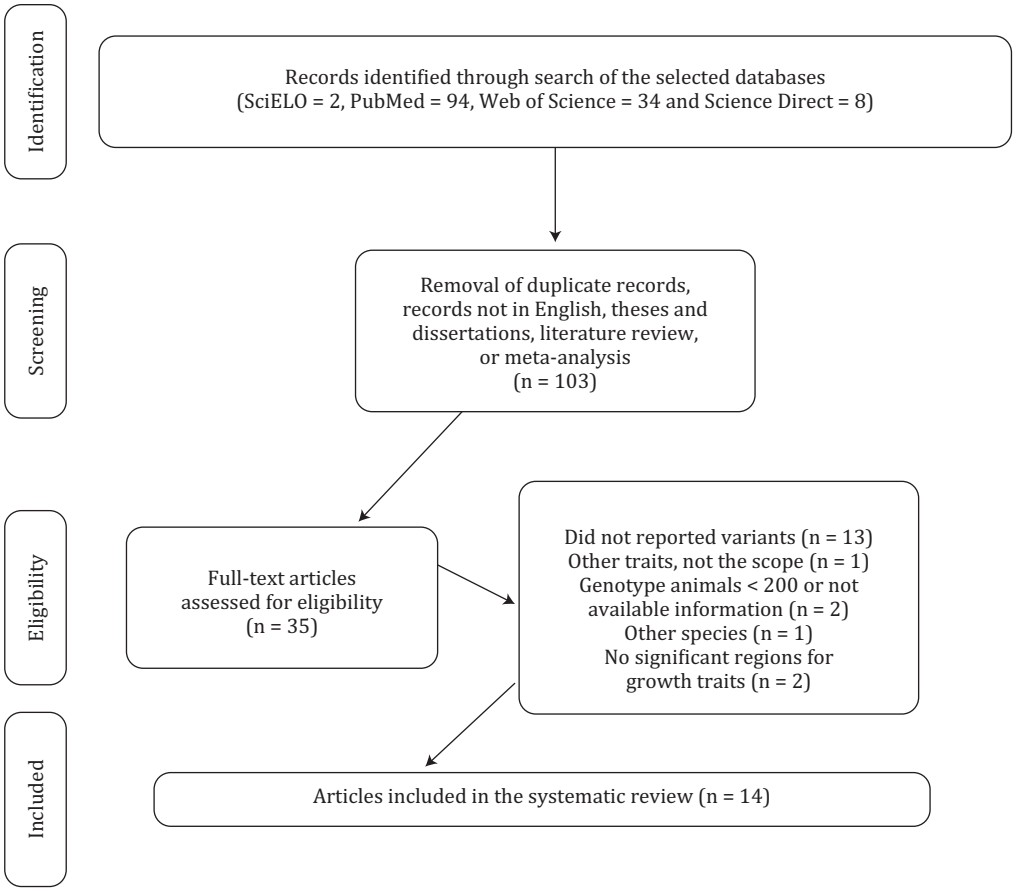
Therefore, the inclusion criteria for the systematic review was: scientific papers addressing weight gain and growth traits in sheep; written in English; original scientific papers; ≥ 200 genotyped animals; and GWAS using SNP panels or haplotypes. Duplicate papers, papers published before 2012, and papers that did not meet the selection criteria were excluded from the database. Scientific papers with no significant regions for the traits evaluated in this study were also removed. Papers that reported just the candidate genes and not the position of significant genomic regions or the SNP names were also excluded (Figure 2). The significant SNP were searched at the ENSEMBL platform (Martin et al., 2023) using the 3.1 Texel assembly. A region of ±250 Kb from the significant SNP was selected to find positional candidate genes using the Biomart tool (Kinsella et al., 2011).

After the mentioned quality control, duplicated genes were removed, and the list with the candidate genes (SNP with P-value ≤ 10^{-6}) was used for the functional annotation clustering and pathway analysis using David v2023q4 (Sherman et al., 2022; Huang et al., 2009), and Clue Go v2.5.10 (Bindea et al., 2009), a Cytoscape v3.10.1 (Shannon et al., 2003) plug-in. For Cytoscape configurations, we used a medium network specificity, a P-value cutoff = 1.0E-4 for the pathways, Kappa Score of 0.5, and the P-value multiple-test correction method used was Bonferroni.

3. Results

3.1. Meta-analysis of genetic parameters

Table 1 shows the descriptive statistics and abbreviations used for the traits evaluated in this study. A higher KR was observed from birth to weaning (18.6), which decreased with age (e.g., 18.63 for KR 0-3 to 6.63 for KR 3-6). The coefficient of variation ranged from 7.4% (for KR 0-3) to 52.9% (for ADG 0-3), indicating significant variation across different ages. Six estimates for direct heritability had



Adapted from PRISMA (Moher et al., 2009).

Figure 2 - Flow diagram of the article selection process for the systematic review and functional analysis of candidate genes and metabolic pathways.

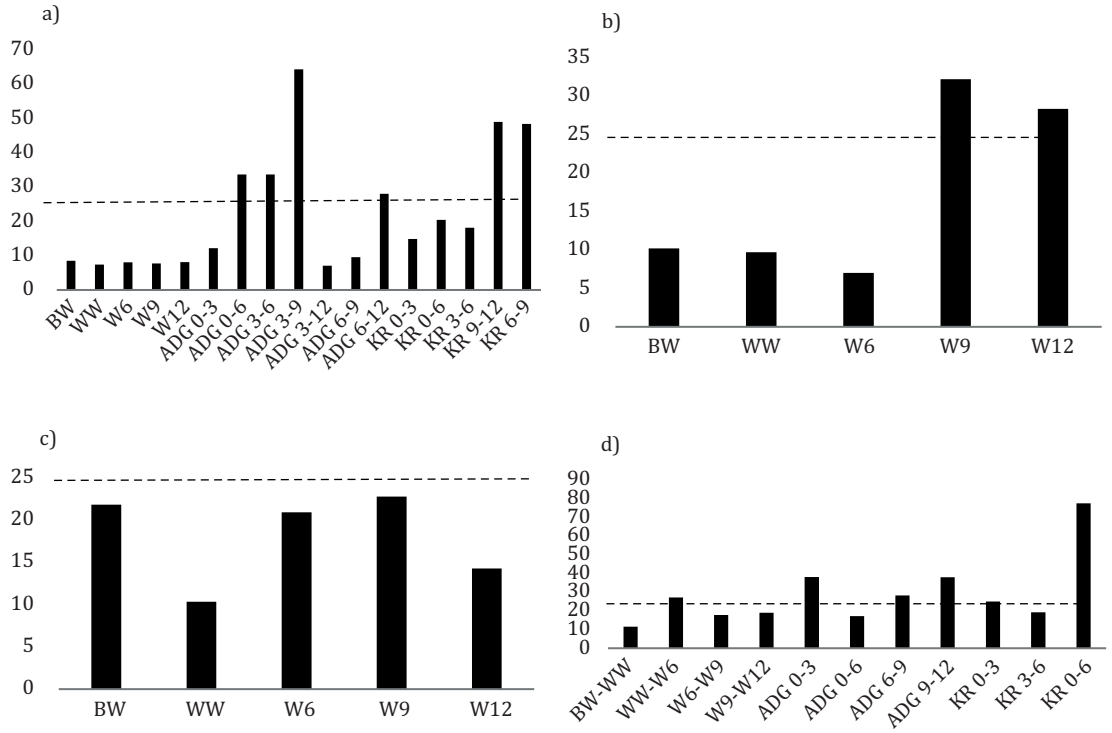
Table 1 - Trait, abbreviation, measurement unit, number of articles, total number of records, mean and standard deviation (SD) of the trait, and coefficient of variation (CV%)

Trait	Abbreviation	Unit	No. of articles	No. of records	Mean	SD	CV%
Birth weight	BW	kg	89	624,861	3.77	0.67	17.83
Weaning weight	WW	kg	78	593,675	18.13	4.94	27.28
Weight at 6 months	W6	kg	41	158,637	25.19	7.34	29.15
Weight at 9 months	W9	kg	31	90,098	28.80	9.05	31.42
Weight at 12 months	W12	kg	34	87,092	33.32	10.46	31.40
Average daily gain from birth to three months	ADG 0-3	g	23	73,326	145.17	76.85	52.94
Kleiber ratio from 0 to 3 months	KR 0-3	-	14	64,330	18.63	1.38	7.43
Kleiber ratio from 3 to 6 months	KR 3-6	-	9	31,927	6.63	1.82	27.55
Kleiber ratio from 0 to 6 months	KR 0-6	-	4	12,981	9.68	3.81	39.43

RSE higher than 25% (Figure 3): ADG from birth to six months of age (ADG 0-6), ADG from three to six months of age (ADG 3-6), ADG from three to nine months of age (ADG 3-9), KR from nine to three months (KR 9-3), and KR from six to nine months (KR 6-9). Therefore, two estimates for maternal heritability (W9 and W12) and three correlations (ADG birth weight × weight at three months, ADG weight at nine months × weight at 12 months, and KR birth weight × weight at six months) were removed from the study (Figure 3). The traits that were discarded based on RSE had proportionally higher direct heritabilities and correlations because of the small number of articles and wide variation in the values of the traits.

The heritability estimates found for the evaluated traits were generally low to moderate, with small variation observed (ranging from 0.07 to 0.29; Table 2). The between-study heterogeneity was high (I^2 > 75%) for most traits, except for the KR from three to six months (KR 3-6). Estimates of direct heritabilities for weight ranged from 0.18 to 0.29 for weights measured at birth weight (BW) and nine months (9W) of age, respectively. Direct heritability for KR estimates ranged from 0.09 to 0.17 for KR evaluated from birth to weaning and from birth to six months (Table 2).

In general, the maternal heritability estimates showed low variation, from 0.07 (WW) to 0.16 (BW). On the other hand, total heritability was only estimated for growth traits, i.e., weights measured from birth to 12 months of age. Total heritabilities generally had low magnitude and range interval among traits, ranging from 0.18 for BW and 9W to 0.21 for 6W. The pooled genetic correlation estimates were in general positive and had moderate to high magnitude. Moreover, all estimated correlations showed high between-study heterogeneity (I^2 > 75%; Table 3). The genetic correlations were positive and had moderate to high magnitude (ranging from 0.45 to 0.53). The highest correlations were observed at older ages, specifically for W9 × W12 (0.53) and WW × ADG 0-6 (0.53).



Heritabilities and correlations with RSE higher than 25% were excluded from the meta-analysis.
BW - birth weight; WW - weaning weight; W6 - weight at six months of age; W9 - weight at nine months of age; W12 - weight at 12 months of age; ADG 0-3 - average daily gain from birth to three months of age; KR 0-3 - Kleiber ratio from birth to three months; KR 3-6 - Kleiber ratio from three to six months; KR 0-6 - Kleiber ratio from birth to six months.

Figure 3 - Relative standard error (RSE) for (a) direct heritability, (b) maternal heritability, (c) total heritability, and (d) genetic correlation.

All covariates studied explained less than 60% of heterogeneity between-study (r^2<60%; Table 4). The year of data collection, statistical method (REML or Bayesian), type of analysis (i.e., single, two, or multiple-trait), and latitude (between tropics or outside tropics) were the covariates that most affected the grouped heritability estimates in lambs of different ages. The highest r^2 values were recorded for the direct heritability of KR 0-3 and the maternal heritability of W6 (56 and 58%, respectively), explained by latitude and the statistical method, which explained 52.4% of the difference observed between studies for the effect size of direct heritability of BW. Overall, the r^2 statistics were low for most of the evaluated covariates across traits.

Table 2 - Number of contributing articles for the direct, maternal, and total heritabilities (N, N_{mat}, and N_{total}, respectively); direct, maternal, and total heritabilities (h^2, h^2_{mat}, and h^2_{total}, respectively) estimated using a random effects model; 95% confidence interval for direct, maternal, and total heritabilities (95% CI, 95% CI_{mat}, and 95% CI_{total}, respectively); and I^2 index to test the heterogeneity of direct, maternal, and total heritabilities (I^2, I^2_{mat}, and I^2_{total}, respectively) for each trait analyzed

Trait	N	h^2	95% CI	I^2 (%)	N_{mat}	h^2_{mat}	95% CI_{mat}	I^2_{mat} (%)	N_{total}	h^2_{total}	95% CI_{total}	I^2_{total} (%)
BW	82 (82)	0.18	0.16-0.21	99.05	39 (39)	0.16	0.13-0.18	99.95	17 (17)	0.18	0.16-0.20	99.89
WW	71 (79)	0.20	0.18-0.24	99.96	33 (34)	0.07	0.06-0.09	77.18	24 (24)	0.19	0.15-0.23	99.93
W6	38 (39)	0.25	0.22-0.30	99.99	20 (20)	0.12	0.07-0.17	99.99	14 (14)	0.21	0.17-0.26	100
W9	31 (31)	0.29	0.25-0.33	99.98	-	-	-	-	10 (10)	0.18	0.09-0.28	99.95
W12	29 (32)	0.26	0.22-0.31	99.98	-	-	-	-	11 (10)	0.20	0.15-0.26	99.70
ADG 0-3	21 (21)	0.24	0.18-0.31	99.99	-	-	-	-	-	-	-	-
KR 0-3	12 (13)	0.17	0.10-0.25	99.98	-	-	-	-	-	-	-	-
KR 0-6	4 (4)	0.09	0.04-0.14	92.86	-	-	-	-	-	-	-	-
KR 3-6	9 (9)	0.10	0.06-0.14	78.69	-	-	-	-	-	-	-	-

BW - birth weight; WW - weaning weight; W6 - weight at six months of age; W9 - weight at nine months of age; W12 - weight at 12 months of age; ADG 0-3 - average daily gain from birth to three months of age; KR 0-3 - Kleiber ratio from birth to three months; KR 3-6 - Kleiber ratio from three to six months; KR 0-6 - Kleiber ratio from birth to six months.

Table 3 - Number of contributing articles (N), genetic correlation between traits (rg), 95% confidence interval (95% CI), and I^2 index for each trait

Trait	N	rg	95% CI	I^2 (%)
BW × WW	26 (29)	0.45	0.30-0.52	99.98
W6 × W9	11 (11)	0.49	0.82-1.37	100
W9 × W12	11 (11)	0.53	0.53-1.65	100
WW × ADG 0-6	4 (4)	0.53	0.32-1.23	98.85
KR 0-3 × WW	5 (5)	0.46	0.15-1.02	95.78
KR 3-6 × WW	5 (6)	0.50	0.15-1.02	94.53

BW - birth weight; WW - weaning weight; W6 - weight at six months of age; W9 - weight at nine months of age; W12 - weight at 12 months of age; ADG 0-6 - average daily gain from birth to six months of age; KR 0-3 - Kleiber ratio from birth to three months of age; KR 3-6 - Kleiber ratio from three to six months of age.

Table 4 - Meta-regression of growth traits in sheep considering the effect of different covariates

Trait	Covariate[1]	r^2 (%)
BW (direct h^2)	Statistical method	52.4
BW (direct h^2)	Latitude	52.4
WW (total h^2)	Type of analysis*	55.8
W6 (maternal h^2)	Year*	58
KR 0-3	Latitude*	56

BW - birth weight; WW - weaning weight; W6 - weight at six months of age; W9 - weight at nine months of age; W12 - weight at 12 months of age; KR 0-3 - Kleiber ratio from birth to three months of age.
[1] Statistical method - REML or Bayesian; Latitude - between or outside tropics; Year - (1960-1980) year 1, (1981-2000) year 2, and (2001-2022) year 3; Type of analysis - uni-, bi-, or multivariate.
* Significant covariates (P<0.01).

3.2. Systematic review and functional analysis of candidate genes and metabolic pathways

After quality control, 14 articles remained for the systematic review (Supplementary material S3). These papers reported significant genomic regions associated with body weight at different ages, metabolic adult weight, body condition score, daily gain at different ages, residual feed intake, growth rate, mature body size, body length, and feed conversion rate. The breeds varied across papers; however, the most representative were Hu (21.4%), followed by Texel (14.3%) and Scottish Blackface (14.3%). After excluding duplicated genes, 461 positional candidate genes were identified in the significant regions, distributed across all sheep genome. Of these, 364 and 458 genes were recognized by David and Cytoscape, respectively.

The four most significant clusters had an enrichment score greater than 2.0 (Table 5). Terms 1, 2, 3, and 4 included 13, 11, 7, and 3 genes, respectively, totaling 34 genes grouped in these four main GO terms. Figure 4 presents a summary of the top 10% of the most significant terms enriched by ClueGo, directly related to growth an embryonic development.

Table 5 - Gene Ontology analysis of growth-related traits in sheep (with Enrichment Score > 2.0)

Top functional group[1]	Top GO term[2]	Clustered gene	ES[3]	P-value
1	Trace-amine receptor activity	*W5PY76_SHEEP, LOC101102987, LOC101101992, TAAR1, TAAR5, LOC101104757, LOC101104500, LOC101119483, LOC101103241, LOC101103482, LOC101103730, LOC101118960, LOC101119225*	4.74	3.3E-19
2	Homeobox_metazoa	*W5PII1_SHEEP, EVX1, HOXB1, HOXB2, HOXB3, HOXB4, HOXB5, HOXB6, HOXB7, HOXB8, HOXB9.*	2.94	3.0E-6
3	ANF_lig-bd_rcpt	*W5P1E4_SHEEP, W5P179_SHEEP, W5PYC4_SHEEP, GABBR1, GRID2, GRM1, GRM7*	2.12	7.6E-5
4	Arachidonate 12-lipoxygenase activity	*ALOX12, ALOX15, LOC101113251*	2.04	1.2E-3

[1] Based on the highest enrichment score.
[2] Based on the P-value.
[3] Enrichment score.

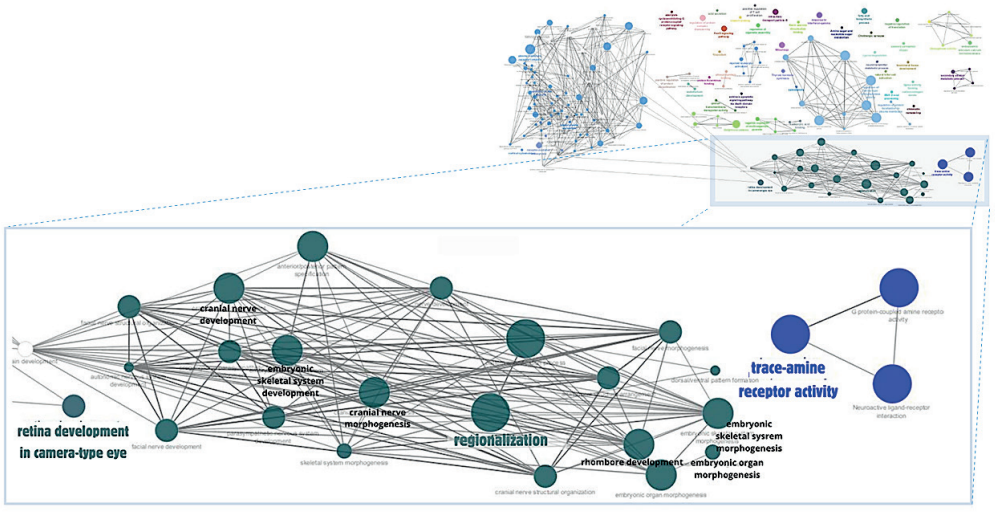


Figure 4 - Top 10% most significant molecular pathways associated with growth and embryo development.

4. Discussion

4.1. Meta-analysis of genetic parameters

Phenotypic averages obtained in this study (Table 1) were slightly greater than those obtained by Ahmad et al. (2021), who worked with Corriedale sheep in India (average BW, WW, W6, W9, and W12 of 3.7, 13.2, 18.6, 22.2, and 25.8 kg, respectively). Haile et al. (2020) used tropical breeds known for their adaptability to the hostile environment and low body weight. In this study, the following breeds that are usually raised in tropical regions were used for analysis: Morada Nova, Suffolk, Corriedale, Dorper, Romney Marsh, Santa Inês, and Texel. Consequently, their average weights at six months were lower than the ones observed in this study (their six-month weights were estimated as 21.60 ± 0.20, 16.5 ± 0.54, and 14.0 ± 0.04 kg for the Bonga, Horro, and Menz breeds, respectively). The KR has been used as a selection criterion for growth efficiency, being an indicator of feed conversion. According to Kleiber (1947), a higher KR reflect better feed conversion in animals. This measure can be used to assess average feed intake. Additionally, KR is expected to decrease with advancing age due to a decline in feed conversion efficiency. It is expected that the KR decreases with advancing age due to the decrease in food conversion (Kleiber, 1947). In the present study, it was possible to observe a greater KR in the period from birth to weaning (18.6; Table 1), which decreased with age (e.g., 6.6 for KR 3-6; Table 1). Similar results were reported by Dhaka et al. (2023) working with Sonadi lambs in India (e.g., they reported 15.25 for KR measured from birth to weaning and 3.84 from weaning to six months post-weaning, respectively).

In this study, the coefficient of variation ranged from 7.4 (for KR 0-3) to 52.9 (for ADG 0-3). The wide confidence intervals estimated suggest the high variation between studies (Table 1). In meta-analysis studies, this coefficient can be used as a complementary measurement for the I^2 statistic, indicating the variability of the data obtained in relation to the mean; the higher the value, the greater the heterogeneity between studies (Cairns and Prendergast, 2022).

The between-study heterogeneity was high ($I^2 > 75\%$) for most traits. This statistic assesses how much variability in the effect size is due to differences between studies in the outcomes compared to chance, i.e., by the sampling error, for all traits and parameters evaluated (Table 2).

As expected, the estimated confidence intervals for direct heritability were generally wider (0.04 to 0.31) than those obtained in individual published studies (0.03 to 0.14) (Prakash et al., 2020). Heritabilities were generally low to moderate (0.09 to 0.29; Table 2), with higher values of direct heritabilities for weight traits evaluated in later ages (W9). This effect is likely associated with a smaller maternal effect and, consequently, with a greater impact of the animal's direct genetics as the animal ages. Furthermore, it is worth noting that lamb performance is also influenced by the maternal genetic effects; thus, maternal heritability was estimated only for the early growth traits (i.e., BW to weight at six months of age). However, this trend was not observed for KR, which decreased over time. This result may be due to the decrease in KR with age, which could reduce the genetic variance and, consequently, heritability. In the review performed by Safari et al. (2005), the weighted average heritabilities for growth traits were generally moderate in magnitude, ranging from 0.15 to 0.41. Murphy et al. (2018), working with East Friesian and Lacaune sheep, estimated direct and maternal heritabilities for BW as 0.27 (±0.04) and 0.25 (±0.02), respectively. These estimates were slightly higher than the ones observed in the present study (i.e., 0.18 and 0.16). Studying Indian Corriedale sheep, Ahmad et al. (2021) reported direct heritabilities for BW, WW, W6, W9, and W12 as 0.13 (±0.023), 0.30 (±0.029), 0.29 (±0.030), 0.19 (±0.025), and 0.16 (±0.024), respectively, which were generally lower than those estimated in the present study (Table 2). Nonetheless, the low to moderate heritabilities suggest that most of the trait variation is not due to the additive genetic of the lamb itself, but rather, to environmental factors that contributed to birth weight.

Bangar et al. (2018) evaluated KR in Deccani sheep at weaning and six months of age and estimated heritabilities of 0.04 (±0.04) and 0.16 (±0.06), respectively. On the other hand, Kumar et al. (2018)

obtained heritability estimates for KR in sheep at different ages, which ranged from 0.17 (±0.06) to 0.25 (±0.07) and were more in line with the ones estimated in the present study (Table 2). Similarly, Ambike et al. (2022) also estimated direct heritability in a meta-analysis for sheep in the tropics for KR 3-6 and 18-month weights, which ranged from 0.04 to 0.38, respectively.

Genetic correlations were positive and had moderate to high magnitude (ranging from 0.45 to 0.53; Table 3). As expected, the genetic correlations between weights measured at closer ages were higher than the correlations estimated for weights measured at ages that are more distant. The highest correlations were observed at older ages, i.e., for W9 × W12 (0.53), and WW × ADG 0-6 (0.53), which may be related to the reduction in the effect of the dam (Gathura et al., 2020). The moderate correlation between WW and ADG 0-6 suggests that selection could be performed for WW in early stages (~3 months), expecting higher gains for ADG at more advanced ages. Recent meta-analyses of genetic parameters in sheep have also reported genetic correlations. For instance, Medrado et al. (2021) reported genetic correlations ranging from 0.45 (BW × W9) to 0.90 (WW × W6), and Ambike et al. (2022) reported correlations ranging from 0.42 (BW × ADG 0-3) to 0.90 (W6 × KR 0-3).

Castro (2001) recommended analyzing the causes of variation found in meta-analysis studies using a meta-regression. The results for traits with a coefficient of determination $r^2 \geq 50\%$ (Table 4) indicated that a moderate amount of heterogeneity was captured (Harrer et al., 2021). Meta-regression was used to explore the main sources of variation among response variables, revealing that the main causes of heterogeneity between studies were related to the year of data collection, continent, latitude, type of analysis, and statistical method.

In summary, the heritability estimates tended to increase over the years for WW and W6, with the highest heritabilities estimated for the year group 3 (2000-2019), representing more recent years ($P<0.01$). This trend explains 58% of the difference observed in Table 4. One possible explanation for this finding might be related to the improvements in system production over the years, decreasing environmental variation and, consequently, increasing heritability estimates. Additionally, the inclusion of genomic information in recent years has likely contributed to higher genomic evaluation accuracies (e.g., Almasi et al., 2021). This, in turn, can result in increased heritabilities, as a greater portion of the variation is now captured by the markers, rather being assigned to unknown factors (Goddard and Hayes, 2009).

Interestingly, latitude has also affected the KR 0-3 and BW heritabilities, accounting for 52.4% of the variability observed (Table 4). For instance, the highest direct heritability values were observed for BW and KR 0-3 (0.37 and 0.38, respectively) in temperate regions (i.e., Sirinka and Kenya, respectively). This can be attributed to the more stable environments in temperate regions, which typically experience less extreme fluctuations in temperature, humidity, and pasture availability. This stable environment allows the genetic expression of growth traits to be more evident, leading to higher heritability estimates. In contrast, tropical regions are characterized by harsher environmental conditions such as high temperatures, high humidity, heat stress, presence of parasites, and seasonal variations in pasture quality that introduce significant uncontrolled environmental variation. This may increase the environmental component of the phenotypic variation, thereby reducing the proportion attributed to additive genetic variation and, consequently, the heritability estimates. Furthermore, in tropical regions, genotype × environment interactions are more pronounced, affecting the expression of genes related to growth, i.e., the same genotype may perform differently under changing environmental conditions, diluting the observed additive genetic effect (Hoffmann, 2010; Ojango and Pollott, 2002).

The method used (REML or Bayesian) explained 52.4% of the difference observed between studies for the direct heritability effect sizes of BW (Table 4). This result shows that the choice of statistical method influenced the variation in heritabilities for growth traits in sheep across the different studies. Bayesian methods use prior probability distributions that can influence the final estimates. These methods are often more robust in situations with limited data or complex traits, which can contribute to slightly higher estimates (Balasundaram et al., 2023a), which is in agreement with our results for WW (0.27 vs 0.20, for Bayesian and frequentists methods, respectively). However, despite its importance

to explain the between-study heterogeneity, this covariate was not significant (P>0.01). Most studies in literature show small difference between heritability estimates by using Bayesian or frequentist approaches (Choudhary et al., 2022; Balasundaram et al., 2023a; Balasundaram et al., 2023b). This explains 58% of the difference observed in Table 4.

The type of analysis (single, two, or multiple-trait) (P<0.01), also explained 55.8%, a significant proportion, of the between-study variability observed for some traits. For example, analyzing the heritability of WW, the r^2 was 55.8% for this covariate, with a tendency towards higher values in univariate analysis. Studying growth traits in beef cattle, Cardoso et al. (2001) found that univariate analysis tends to provide higher heritabilities when compared with other analyses. For growth traits, especially weights evaluated at different ages, the use of two or multiple-trait models may be advantageous because they utilize additional information from the correlations between traits, that are generally moderate to high for sheep, which may reduce bias and improve the accuracy of genetic parameter estimates (Ahmad et al., 2021).

Regarding the genetic correlations, the between-study variation observed for the correlation between BW × WW was influenced by the year of data collection, tending to increase over the years, but this trend was not significant (P>0.01). In addition, analyzing more than one trait together increases the amount of information available, which can contribute to a more accurate estimation of variance components and genetic parameters for the trait. In general, r^2 statistics was generally low for the majority of covariates evaluated across traits, suggesting that unknown factors that were not considered in the present meta-regression may be responsible for the high between-study variability observed across traits.

4.2. Systematic review and functional analysis of candidate genes and metabolic pathways

The complete list of the candidate genes identified in the literature, per chromosome, is available in the Supplementary material S3. Positional candidate genes were located on chromosomes 1, 2, 3, 4, 5, 6, 8, 9, 10, 11, 12, 13, 15, 16, 19, 20, 21, 23, and 24, but the majority of genes were located on chromosomes 11 (n = 83) and 6 (n = 52).

David analysis was able to cluster the 364 genes in 36 clusters. Table 5 summarizes the results for the top four most significative clusters, i.e., those that presented an enrichment score higher than 2.0. Top terms 1, 2 3, and 4 harbored 13, 11, 7, and 3 genes respectively, totaling 34 genes harbored in these top 4 Go Terms.

“Trace-amine receptor activity” was identified as the top 1 functional group in the analyses performed using David (Table 5) and Cytoscape (Figure 4). This GO Term is associated with weight gain in pregnant women (Ludwig-Słomczyńska et al., 2021). Trace-amine genes play a crucial role in the regulation of neuroendocrine mechanisms. They act in the brain to decrease food intake and increase feelings of satiety, reduce fasting glucose in the liver, increase insulin production in the pancreas, and decrease gastric emptying and glucose excursion (Berry et al., 2017). Genes grouped in this pathway are located in the OAR8, between 57.6 to 57.9Mb. The “Homeobox_metazoa” group was identified as the second most significant functional group in the David analysis (Table 5). This GO term harbored the *HOX* gene family (i.e., *HOXB2*, *HOXB3*, *HOXB4*, *HOXB5*, *HOXB6*, *HOXB7*, *HOXB8*, *HOXB9*), which plays an important role in development and cell differentiation in several mammalian species (Byrne et al., 2014; Zhang et al., 2023). The HOXB genes were located at the OAR11, at 37.3 Mb.

“ANF_lig-bd_rcpt” also known as “Receptor, ligand-binding region”, was the third most significant group identified in the functional analysis (Table 5). This domain is an extracellular ligand-binding region of several types of receptors (Kuryatov et al., 1994), which includes receptor ligand-binding genes and three glutamate receptors (*GRID2*, *GRM1*, *GRM7*). In an experiment with mice, Duvoisin et al. (2005) found that mice lacking in metabotropic glutamate receptor 8 were 8% heavier than the wild-type mice. Xu et al. (2013) also found that problems with glutamate receptors in adult mice neurons lead to obesity. Genes in this pathway are distributed across the OAR8, 19, 20, and 21. Both “Trace-amine

receptor activity" and "ANF_lig-bd_rcpt" clustered genes from the G-protein-coupled receptor families: the first one is from family 1 (*W5PY76_SHEEP*), and the second is from family 3 (*W5P1E4_SHEEP*). The G-protein-coupled receptors are a large family of transmembrane receptors involved in recognizing signal pathways, such as the cAMP signal pathway. These genes are involved in a range of biological functions, including endocrine functions. "G-protein-coupled amine receptor activity" was the second most significant term enriched in the Cytoscape analysis, along with other pathways associated with endocrine and energetic metabolism functions (Vassart and Costagliola, 2011).

Arachidonate 12-lipoxygenase activity was the fourth most significant group identified in the functional analysis performed by David (Table 5). The arachidonate 12-lipoxygenase activity is a pathway directly related to lipidic metabolism, which is essential for cell maintenance and embryo and early life development (Innis, 1991). The *ALOX12* gene (i.e., arachidonate 12-lipoxygenase, 12S type) was one of the genes enriched in this pathway, and it codes for the enzyme arachidonate 12-lipoxygenase, which catalyzes the degradation of polyunsaturated fat acid (Sabbir et al., 2021). This pathway has been previously identified as significant for sheep (Posbergh and Huson, 2020) and pork quality traits (Zappaterra et al., 2019; Ding et al., 2022). The three genes enriched in this pathway were located in the OAR11, at 11.4Mb.

In the Cytoscape analysis, the genes were clustered in several roles (Figure 4 and Supplementary material S4). For discussion, we will focus on the top 10% most significant pathways (i.e., 22 GO terms). The "Trace-amine receptor activity" was identified as the top 1 functional group in both Cytoscape and David analysis, and therefore, it will not be further discussed here.

The pathways "Regionalization", "Pattern specification process", "Anterior/posterior pattern specification", and "Embryonic skeletal system development" ranked 4th, 6th, 13th, and 20th, respectively, and were also identified by Muroya et al. (2013). This study identified differentially expressed miRNA in the semitendinosus and masseter muscles in Japanese cattle, suggesting that these genes are related to tissue formation and are involved in developmental processes. The terms "Regionalization" (top 4), "Anterior/posterior pattern formation" (top 13), "Morphogenesis of embryonic organs" (top 15), "Development of the embryonic skeletal system" (top 20), and "Morphogenesis of the embryonic skeletal system" (top 22), related to the development of human abdominal and gluteal subcutaneous adipose tissue deposits, were also found in the study performed by Karastergiou et al. (2013).

The serpin family (serine proteinase inhibitors), known for regulating proteinases involved in various cellular processes such as inflammation and cell death and development, was also identified as significant in the Cytoscape analysis. The main processes involved were: regulation of serine-type peptidase activity, regulation of serine-type endopeptidase activity, negative regulation of serine-type peptidase activity, negative regulation of serine-type endopeptidase activity, and inhibitory activity of serine-type endopeptidase. These processes were ranked 7th, 8th, 9th, 10th, and 11th, respectively. Some of these terms were also observed in the gene ontology analysis carried out by Jung et al. (2015), in a study that evaluated whole-genome expression levels of neonatal mice, suggesting that regulation of Serpin family members may have a role in preventing gastrointestinal cell necrosis.

In the study carried out by Zou et al. (2023), using Duan and Nubia goats, differences in gene expression modification during the development of the *longissimus dorsi muscle* were detected. Upregulated differentially methylated genes were found related to "Morphogenesis of embryonic organs" (top 15), "Development of the embryonic skeletal system" (top 16), and "Morphogenesis of the embryonic skeletal system" (top 21). In the present study, these genes were also significant in the analysis carried out by Cytoscape, showing that there is an important association of these genes in regulating muscle development.

Similarly, Maron (2012) identified pathways associated with the development of cranial nerves (top 16) and morphogenesis of cranial nerves (top 21), studying the main regulatory genes in human neonatal saliva involved in the success of oral feeding. Karpinski et al. (2014) reported that dysphagic symptoms, including decreased weight gain during early postnatal life in mice, are prefigured by altered expression and patterning of genes in embryonic domains that generate the cranial nerve

structures critical for feeding and swallowing. These studies reinforce the association between the development of cranial nerves and growth.

We evaluated pleiotropic genomic regions, i.e., those that were significant for more than one trait. Most of the pleiotropic genes identified in this study were associated with body growth traits in sheep, assessed at different developmental stages (as shown in the Supplementary material S5). Specifically, genes *ENSOARG00000018261* and *ENSOARG00000018241* were found in significant regions associated with post-weaning average daily gain and body weight at 180 days of age, located on OAR6:31029166. We also confirmed the involvement of similar genes located from OAR21:6218306 to OAR21:6291512, from OAR6:31029166 to OAR6:36655091, from OAR6:37057090 to OAR6:37694564, and from OAR15:71950190 to OAR15:71950247. These findings align with our meta-analysis results, showing moderate to high genetic correlations between growth traits at different ages (0.45 – 0.53).

5. Conclusions

Heritability of growth traits in sheep ranged from low to moderate, while the genetic correlation among traits ranged from moderate to high magnitude. These low heritabilities suggest the existence of large environmental effects and several genes with small effect affecting the phenotypic expression of the traits. This is consistent with the number of genes found in significant regions located across almost all chromosomes in the sheep genome, as observed in the systematic review. The significant genomic regions related with sheep growth traits were mainly located on chromosomes 11 and 6; some of these regions are equal across traits, indicating presence of pleiotropic genes. Functional pathways revealed mechanisms related with tissue formation and skeletal system development.

Supplementary material

The supplementary material of this article can be found online at: https://www.rbz.org.br/wp-content/uploads/articles_xml/1806-9290-rbz-54-e20240124/1806-9290-rbz-54-e20240124-suppl.zip

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author contributions

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Conflict of interest

The authors declare no conflict of interest.

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