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GENETIC INFLUENCE OF GROWTH HORMONE RECEPTOR (GHR) POLYMORPHISMS ON RABBIT BODY WEIGHT: A META-ANALYSIS

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Growth and metabolism regulation in rabbits are influenced by the growth hormone receptor (*GHR*). However, despite its promising potential as candidate for marker assisted section, the association between *GHR* gene polymorphisms and body weight under different genetic models remains inconclusive. This study deployed systematic review and meta-analysis to assess this relationship. The protocol was retrospectively registered on the Open Science Framework. Following the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines, 17 data points from six studies were analyzed. Hardy-Weinberg Equilibrium (HWE) was tested, and four genetic models (co-dominant, dominant, recessive, and over-dominant) were fitted using OpenMeta® Analyst Software. Standardized mean differences (SMDs) were estimated using Cohen's d method, with heterogeneity assessed via Q statistic, Tau-squared (τ^2), H-squared (H^2), and I-squared (I^2). Egger's regression test was used to evaluate publication bias and sensitivity analysis was conducted to determine single-study effects. There was significant association ($p<0.05$) of *GHR* gene with body weight of rabbits under one of the co-dominant models (CG vs GG). However, this association was not significant ($p>0.05$) under all other genetic models. Further, the results indicated that GG genotype had higher body weight than CG genotype. However, there was no difference ($p>0.05$) between CC and CG and CC and GG genotypes. This suggests that *GHR* gene polymorphisms have a limited influence on body weight and their impact may depend on specific genetic models.

Key words: Candidate genes, genetic markers, genetic models, meta-analysis, SNP analysis

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INTRODUCTION

According to OSENI and LUKEFAHR (2014) and SIDDIQUI *et al.* (2023), rabbits contribute significantly to ensuring food security in developing countries due to their adaptation to diverse environmental conditions, ability to survive on forages only, high prolificacy and short generation interval. However, variations in the growth performance traits of rabbits have been reported by various authors, including ATTIA *et al.* (2013), KHAN *et al.* (2016), SOMMERVILLE *et al*. (2017), OSENI *et al*. (2021), and BIROLO *et al*. (2022). These variations are primarily attributed to environmental and genetic differences (GHOSH *et al.*, 2010; CASTO-REBOLO *et al.*, 2021). Therefore, genetic improvement of rabbits, especially in developing countries, is essential.

Genetic improvement of rabbit is a critical aspect of breeding programs aimed at enhancing growth, survival and productivity. In particular, growth performance traits in rabbits such as body weight and average daily weight gain are key determinants of productivity and economic viability. These traits directly influence meat yield, feed conversion efficiency, and overall profitability. As an alternative to traditional breeding programs, selective breeding incorporating marker-assisted selection has been suggested to accelerate this genetic improvement (HELAL *et al.*, 2021; GOSWAMI *et al.*, 2025). However, in order to incorporate marker assisted selection, it is important to identify candidate genes that could be used as genetic markers for economically important traits such as body weight in rabbits (DEHKHODA *et al.*, 2018). Among such candidate genes, the growth hormone receptor (*GHR*) gene has garnered significant research interest due to its crucial role in mediating the physiological effects of growth hormone on growth, metabolism, and body composition (HERRINGTON and CARTER-SU, 2001). According to Ramadan *et al*. (2020), the interplay between growth hormone, the growth hormone receptor, and insulin-like growth factors is integral to the coordination of growth regulation in rabbits. The activation of the growth hormone receptor occurs when growth hormone binds to its receptor, triggering a cascade that includes the activation and expression of insulin-like growth factors and other genes (HERRINGTON and CARTER-SU, 2001). This process, as detailed by DEHKHODA *et al*. (2018), leads to the stimulation of amino acid uptake and protein synthesis, which are essential for growth and development.

Various studies have shown that single nucleotide polymorphisms (SNPs) in the *GHR* gene are associated with variations in body weight across different rabbit breeds (DENG *et al.*, 2008; ZHANG *et al.*, 2012; FONTANESI *et al.*, 2016; GENCHEVA *et al.*, 2022). Additionally, three genotypic variants of the *GHR* gene (CC, CG, and GG) have been identified in rabbits. However, reports on the relationship between these genotypes and body weight have been inconsistent, with some studies showing significant associations while others do not. For example, some studies, like DENG *et al*. (2008) and FONTANESI *et al*. (2016), found that GG genotypes had higher body weights, while others, such as ZHANG *et al*. (2012) and GENCHEVA *et al*. (2022) reported that CC genotypes were heavier. Meanwhile, HELAL (2019) and MIGDAL *et al*. (2019) observed no significant differences at certain ages but noted variations at specific growth stages. Thus, it is important to conclusively understand the relationship between these genotypic variants and body weight for potential application in marker-assisted selection in rabbits. Therefore, the objective of this study is to evaluate the relationship between the *GHR* gene polymorphisms and body weight in rabbits using meta-analysis. Our hypothesis was that one or more of the polymorphic variants would be associated with heavier body weight.

MATERIALS AND METHODS

Database and search strategy

This study was retrospectively registered on the Open Science Framework (OSF) under registration DOI [https://doi.org/10.17605/OSF.IO/FU6JY]. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (MOHER *et al.*, 2009) was used to conduct a thorough database search as presented in Figure 1.

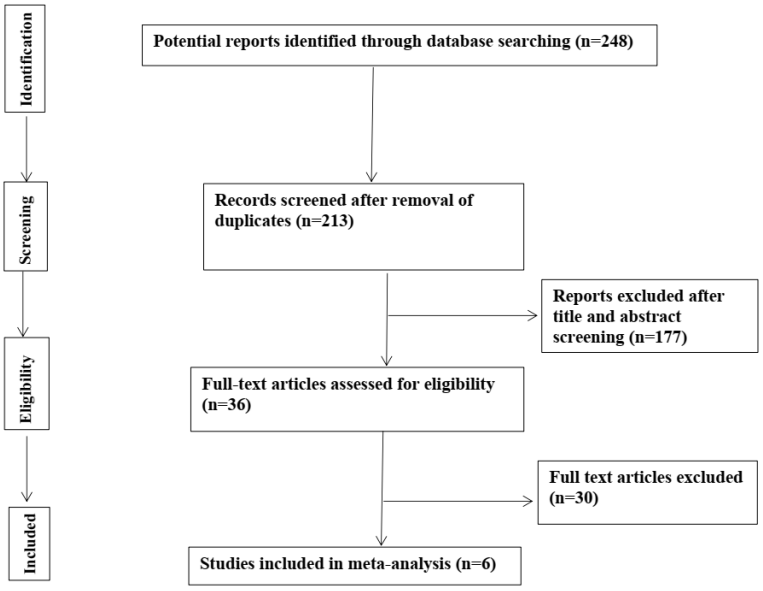


Figure 1. PRISMA flow diagram illustrating the study selection process

Initial screening of all studies identified through database search was based on predefined eligibility criteria. Titles and abstracts of all identified articles were screened, and relevant studies were selected for detailed evaluation. The electronic database search utilized a variety of keywords and terms, including SNP, growth hormone receptor, association, polymorphism, gene, *GHR*, rabbit, growth performance, body weight, average daily gain, and growth traits. These terms were combined to form search phrases such as "association of growth hormone (*GHR*) gene with body weight and average daily gain of rabbits" and "*GHR* gene in rabbits," among others. A total of 248 articles were retrieved after implementing the search strategy. During the deduplication process, 35 articles were removed. Subsequently, 177 articles were excluded after title and abstract screening for being unrelated. The full texts of 36 articles were assessed for eligibility, and after applying the predefined eligibility criteria, 30 articles were further excluded. Ultimately, six articles were included in the final analysis. These studies were conducted between 2008 and 2022 and originated from China (n=2), Italy (n=1), the Czech Republic (n=1), Egypt (n=1), and Romania (n=1).

Inclusion criteria

The PICO (Population, Intervention, Comparison, Outcome) framework guided the development of these criteria (ERIKSEN and FRANDSEN, 2018). The Predefined eligibility criteria guided the selection process, in line with the PRISMA checklist, to determine whether a study was suitable for inclusion in the meta-analysis. Studies were included if they met the following requirements: they reported polymorphisms in the *GHR* gene of rabbits, described the effects of the *GHR* gene on rabbit body weight, provided sample sizes along with the number of rabbits per genotype (or genotype ratios), and presented least squares means for body weight by genotype. Additionally, studies were required to report standard deviations or standard errors for each least squares mean estimate for body weight traits. Articles that were review papers or summaries were excluded from the analysis.

Two researchers independently extracted data from each study using the Data Extraction for Complex Meta-Analysis (DECiMAL) Guide described by PEDDER *et al.* (2016). The extracted data included the author's name, year of publication, and country of study, sample size, genotype number, mean body weight, average daily gain, standard deviation, standard error, and significance level.

Data were extracted from each article by two independent reviewers. After extraction, the data were reviewed and reconciled to ensure consistency and accuracy. Data extracted included study identifiers such as author's name, year of publication and country of study, further, data on moderators and covariates

Data Extraction and Analysis

Data analysis was conducted using SPSS® (IBM, 2021) and OpenMeta® Analyst Software (WALLACE *et al.,* 2012). The Hardy-Weinberg Equilibrium (HWE) test was conducted for each study using the freely accessible Gene Calculator software available online at [https://gene-calc.pl/hardy-weinberg-page]. Overall, four standard genetic models (co-dominant, dominant, recessive, and over-dominant) were evaluated (presented in Table 1). For the co-dominant model, three pairwise genotype contrasts (CC vs CG, CC vs GG, and CG vs GG) were analyzed separately, resulting in six analytical contrasts in total. This approach is consistent with previous genetic association meta-analyses, where individual genotype comparisons within the co-dominant framework are evaluated separately to capture potential differential effects between specific genotypic classes (BASHIRU and OSENI, 2025a; BASHIRU and OSENI, 2025b). SPSS software was used to calculate the standardized mean differences (SMDs) using Cohen's d method to determine individual and overall effect sizes. Furthermore, heterogeneity among included studies were assessed using Q statistics, Tau-squared (T^2), H-squared (H^2), and I-squared (I^2) metrics. Forest plots were further generated to visualize the effect size, standard error, confidence intervals, and overall estimates for each study. In addition, the Egger's regression asymmetry test and funnel plots were also conducted to evaluate the existence of publication bias. The OpenMeta® Analyst Software WALLACE *et al.,* 2012) was used to conduct meta-regression which aimed to identify factors contributing to between-study heterogeneity, and sensitivity analysis was performed to assess whether the overall effect size was significantly impacted by any individual study.

Table 1. Genetic models and genotype contrasts used in the meta-analysis of association between GHR gene and body weight of rabbits

Genetic model type	Specific genetic model
Co-dominant	CC vs CG
Co-dominant	CC vs GG
Co-dominant	CG vs GG
Recessive	CC vs CG+GG
Dominant	CC +CG vs GG
Over-dominant	CG vs CC+GG

RESULTS AND DISCUSSION

Hardy-Weinberg equilibrium test

Table 2 presents the Hardy-Weinberg equilibrium (HWE) status of studies evaluated and included for the meta-analysis of association between *GHR* gene polymorphisms and body weight of rabbits. Based on the Benjamini-Hochberg adjusted Hardy-Weinberg p values, all the studies included in the analysis had HW p values greater than 0.05 and were considered to be in HWE. This suggests that the populations analyzed were not subject to strong selection, inbreeding, genetic drift, or genotyping errors that could bias the results (LEAL *et al.,* 2005; WIGGINTON *et al.,* 2005; CHEN *et al.,* 2017; NEÁMATZADEH *et al.,* 2024). Furthermore, this enhances the reliability of the meta-analysis, as deviations from HWE can indicate issues such as population stratification (ABRAMOVS *et al.,* 2020) or technical errors in genotyping (HOSKING *et al.,* 2004), which might distort the association between *GHR* gene polymorphisms and body weight.

Table 2. Examination of Hardy-Weinberg equilibrium in the included studies for meta-analysis of association of GHR gene with body weight of rabbits

Study	HW chi-square value	HW P value	Benjamini-Hochberg Adjusted HW p value
Zhang *et al* 2012b	7.442	0.0212	0.0003
Deng *et al*. 2008e	4.3703	0.1125	0.8435
Helal 2019b	7.3894	0.0248	0.7287
Zhang 2012a	3.2608	0.1958	0.7344
Migdal *et al*. 2019c	2.2614	0.3228	0.9684
Migdal *et al*. 2019b	1.8789	0.3908	1.000
Deng *et al*. 2008b	0.8704	0.6471	1.000
Migdal *et al*. 2019a	0.7798	0.6771	1.000
Zhang *et al*. 2012c	1.0617	0.5889	1.000
Deng *et al*. 2008d	0.4579	0.7953	1.000
Gencheva *et al*. 2022a	0.3141	0.8546	1.000
Deng *et al*. 2008a	0.0056	0.9972	1.000
Fontanesi *et al*. 2016	0.0689	0.9661	1.000
Helal *et al*. 2019a	0.0453	0.9776	1.000
Deng *et al* 2008c	0.2797	0.8695	0.9724

HW- Hardy Weinberg

Heterogeneity tests

Table 3 presents the heterogeneity tests for the meta-analysis of association between *GHR* and body weight of rabbits. The τ^2 ranged from 0.138 (Co-dominant CG vs GG) to 0.217 (recessive model). Similarly, the H^2 values ranged from 2.462 (the co-dominant model CC vs GG) to 4.637 (over-dominant model). The Q statistic also ranged from 18.073 (the co-dominant model CC vs GG) to 57.850 (over-dominant model). The P values for the Chi-square test were significant (P<0.01) for the co-dominant models (CC vs CG and CG vs GG), the recessive model and the over-dominant model. The P values for the Chi-square test were significant (P<0.01) for the co-dominant models (CC vs CG and CG vs GG), the recessive model and the over-dominant model. The I^2 values were high (I^2 >59%, ranged from 59.4% to 78.4%) and thus, all genetic models fitted were considered heterogeneous which indicated that effect size reported by different studies included in the meta-analysis of the association between *GHR* gene polymorphism and body weight of rabbits are due to systematic differences and not solely due to sampling errors (RYAN-MOORE *et al.,* 2020). Potential sources of heterogeneity could include differences in rabbit breeds, environmental conditions, genetic background, sample sizes, and methodologies used in different studies. Furthermore, the significant heterogeneity indicate that random-effects models (REM) may be more appropriate than fixed-effects models for this meta-analysis since REM account for underlying between-study differences (DETTORI *et al.,* 2022; ZHAI *et al.,* 23).

Table 3. Heterogeneity test of genetic models for the meta-analysis of the association between GHR gene and body weight of rabbits

Category	Genetic model	τ^2	H^2	I^2	Chi-square (Q statistic)	P value
Co-dominant	CC vs CG	0.171	2.983	66.5	47.412	<0.001
Co-dominant	CC vs GG	0.202	2.462	59.4	18.073	0.320
Co-dominant	CG vs GG	0.138	2.690	62.8	27.096	0.040
Recessive	CC vs CG+GG	0.217	3.926	74.5	41.739	<0.001
Dominant	CC+CG vs GG	0.189	3.675	72.8	26.164	0.052
Over-dominant	CG vs CC+GG	0.187	4.637	78.4	57.850	<0.001

T^2=Tau-squared; H^2 =H-squared; I^2=I-squared

Estimation of overall effect size

The overall effect size estimates for the meta-analysis of the association between *GHR* gene polymorphism and body weight of rabbits are presented in Table 4. The overall effect size under different genetic models evaluated ranged from -0.288 (co-dominant -CG vs GG) to 0.203 (co-dominant -CC vs CG). There was significant association (P<0.05) of *GHR* gene polymorphism with body weight of rabbits under the co-dominant (CG vs GG) model (SMD= -0.288±0.1229; 95% CI =0.327±0.1362, 95% CI= -0.529 to -0.47; p = 0.019). However, *GHR* polymorphisms showed no significant association (P>0.05) with body weight of rabbit under the co-dominant models (CC vs GG and CC vs CG), recessive, dominant and over-dominant models. The negative significant overall effect size (P<0.05) under the co-dominant genetic model (CG vs GG) indicated that, cumulatively for all studies included in the meta-analysis, GG

genotype had higher body weight than CG genotype. There are contrasting reports on these associations in literature. DENG *et al*. (2008) reported no significant difference between the body weight of CG and GG genotype but the two were significantly higher than CC genotype of Harbin white rabbits in China. FONTANESI *et al*. (2016) reported that 10 different breeds of GG genotype had higher body weight ($P<0.05$) than rabbits of CC and CG genotype. However, GENCHEVA *et al*. (2022) reported that Californian rabbits of CC genotype had higher significant body weight at 35, 70 and 90 days than CG and GG genotypes. HELAL (2019) reported no difference ($P>0.05$) in the body weight of CC, CG and GG genotypes of New Zealand and Baladi Red rabbits in Egypt at 8 weeks of age. However, the author reported that CC genotype had higher body weight than CG and GG genotype at 6, 10 and 12 weeks of age. MIGDAL *et al*. (2019) reported no significant difference ($P>0.05$) in body weight between CC, CG and GG genotype of crossbred New Zealand x Belgian Giant Grey rabbit at day-old, 5 weeks and 12 weeks of age. However, significant higher body weight ($P<0.05$) was reported for GG genotype of Belgian Giant Grey rabbit at 5 weeks of age while no difference was reported at day-old and 12 weeks of age. Similarly, significant higher body weight ($P<0.05$) was reported for CG genotype of Termond White rabbit at day-old while no difference was reported at 5 and 12 weeks of age. ZHANG *et al*. (2012) also reported that CC genotype of Tianfu, Iraq and Champagne rabbit had higher body weight ($P<0.05$) than CG and GG genotypes of these breeds of rabbits.

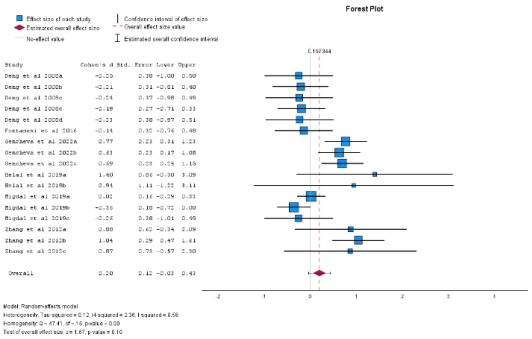
Table 4. Overall effect size estimates for the meta-analysis of the association between GHR gene and body weight of rabbits

Category	Genetic model	Effect size (SMD ±SE)	95% CI	95% PI	P value
Co-dominant	CC vs CG	0.203±0.1331	-0.057 to 0.464	-0.723 to 1.130	0.126
Co-dominant	CC vs GG	0.044±0.1508	-0.252 to 0.339	-0.966 to 1.054	0.772
Co-dominant	CG vs GG	-0.288±0.1229	-0.529 to -0.47	-1.122 to 0.545	0.019
Recessive	CC vs CG+GG	0.126±0.1405	-0.149 to 0.401	-0.911 to 1.164	0.369
Dominant	CC+CG vs GG	-0.170±0.1326	-0.430 to 0.090	-1.139 to 0.799	0.200
Over-dominant	CG vs CC+GG	-0.209±0.1244	-0.453 to 0.034	-1.168 to 0.749	0.092

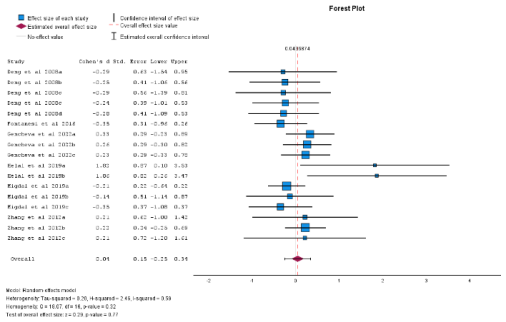
SMD- Standardized Mean difference; SE-Standard error; CI- Confidence interval; PI -Prediction interval

Forest plot of the genetic models for the association between growth hormone receptor gene and body weight of rabbit

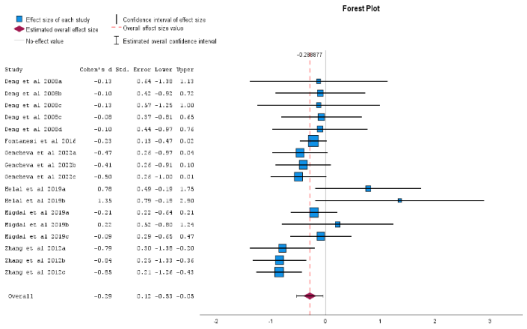
The forest plots illustrating the heterogeneity test for the meta-analysis of the association between the *GHR* gene and body weight of rabbits under various genetic models are shown in Figure 2. These models include the co-dominant model comparisons (CC vs CG and CC vs GG), as well as the recessive, dominant, and over-dominant genetic models. Across all these genetic models, the overall effect size was not statistically significant ($P > 0.05$), indicating no clear association between the *GHR* gene and body weight in rabbits. Most of the effect sizes derived from the studies included in the meta-analysis were close to zero, suggesting that the observed differences in body weight between the compared genotypic groups were not statistically significant. In contrast, Figure 4 presents the forest plot for the heterogeneity test under the co-dominant genetic model comparing CG vs GG genotypes.



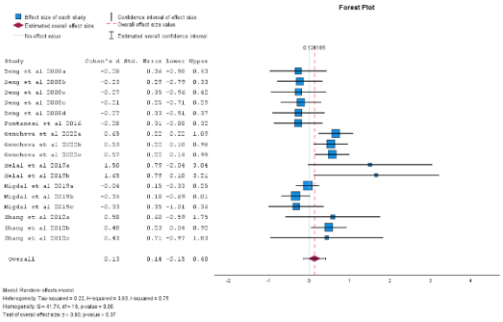
a. Co-dominant model (CC vs. CG)



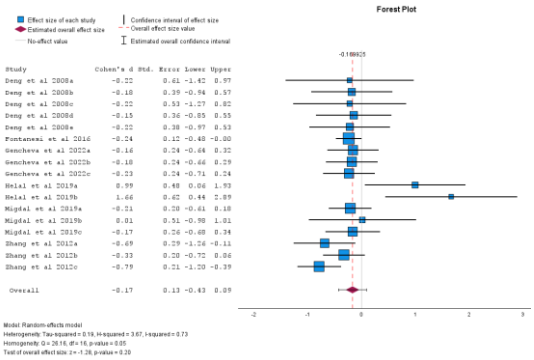
b. Co-dominant model (CC vs. GG)



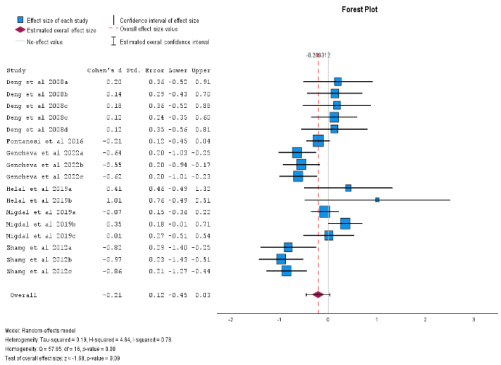
c. Co-dominant model (CG vs. GG)



d. Recessive model (CC vs CG+GG)



e. Dominant model (CC + CG vs GG)



f. Over-dominant model (CG vs CC + GG)

Figure 2. Forest plot of meta-analysis of *GHR* gene association with rabbit body weight under various genetic models

Here, the overall effect size was statistically significant (P < 0.05), demonstrating an association between the *GHR* gene and body weight in rabbits under this specific model. Notably, the effect sizes from most of the included studies did not intersect the vertical null line, indicating that the 95% confidence intervals for these studies did not contain zero. This suggests that the results included in the meta-analysis under this model deviate from the null hypothesis, revealing significant differences in body weight between CG and GG genotypes (P < 0.05).

Egger's regression test for the assessment of publication bias

Table 5 presents the Egger's regression test for the genetic models evaluated. The Egger's regression tests were significant (P<0.05) under the co-dominant (CC vs CG) model [b = 0.806±0.2249; 95% CI= -0.663 to 2.274; P=0.0261], co-dominant (CG vs GG) model [b = -0.617±0.1536; 95% CI= -0.945 to -0.290; P=0.001], recessive model [b = -0.195±0.1314; 95% CI= -0.688 to 0.298; P=0.0413] and over-dominant model [b = -0.715±0.2523; 95% CI= -1.253 to -0.177; P=0.013]. Furthermore, the tests predicted two theoretical missing studies for the analysis under these genetic models and thus suggest the existence of publication bias. Conversely, the Egger's regression-based tests were not significant (P>0.05) under the co-dominant (CC vs GG) model [b = -0.313±0.2904; 95% CI= -0.932 to 0.306; P=0.299] and dominant model [b = 1.825±1.8408; 95% CI= 0.033 to 4.617; P=0.461]. The presence of bias in some genetic models suggests that some studies with negative or non-significant findings might be missing from the literature (BOWDEN *et al.,* 2005), leading to an overestimation or underestimation of effect sizes under these models (LIN *et al.,* 2018; AERT *et al.,* 2019).

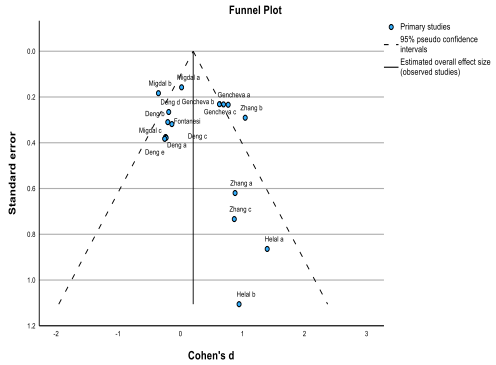
Table 5. Egger's regression test for the assessment of publication bias for the random effects meta-analysis of association between GHR gene and body weight of rabbits

Category	Genetic model	Regression coefficient±SE	95% CI	*p* value	NMS
Co-dominant	CC vs CG	0.806±0.2249	-0.663 to 2.274	0.0261	2
Co-dominant	CC vs GG	-0.313±0.2904	-0.932 to 0.306	0.299	0
Co-dominant	CG vs GG	-0.617±0.1536	-0.945 to -0.290	0.001	2
Recessive	CC vs CG+GG	-0.195±0.1314	-0.688 to 0.298	0.0413	2
Dominant	CC+CG vs GG	1.825±1.8408	0.033 to 4.617	0.461	0
Over-dominant	CG vs CC+GG	-0.715±0.2523	-1.253 to -0.177	0.013	2

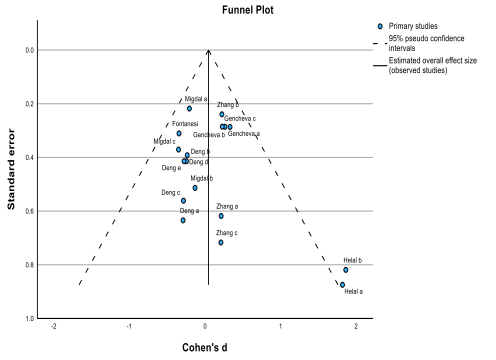
SE- Standard error; CI- Confidence interval; NMS-Number of missing studies

Funnel plots for the assessment of publication bias

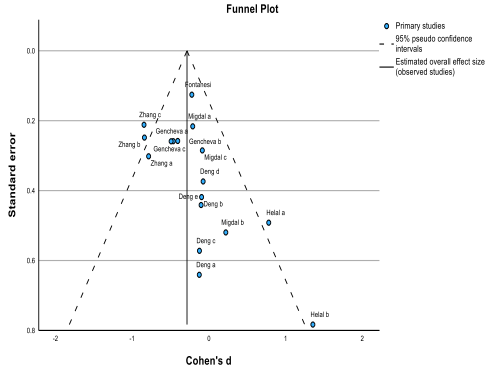
Figure 3 shows the funnel plots of the standard error of effect size for the meta-analysis assessing the association between the *GHR* gene and body weight in rabbits under various genetic models. The plots for the co-dominant models (CC vs. CG and CG vs. GG) exhibited asymmetry, indicating potential publication bias, whereas the funnel plot for the co-dominant model (CC vs. GG) appeared symmetric. Similarly, symmetry was observed in the funnel plot for the dominant genetic model.



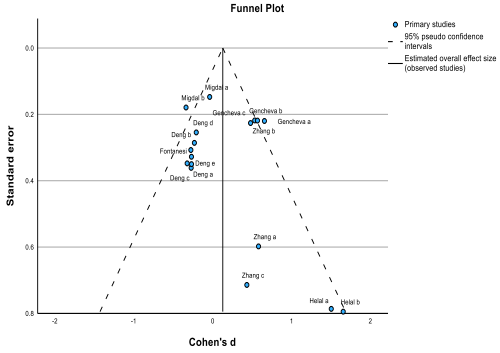
a. Co-dominant model (CC vs. CG)



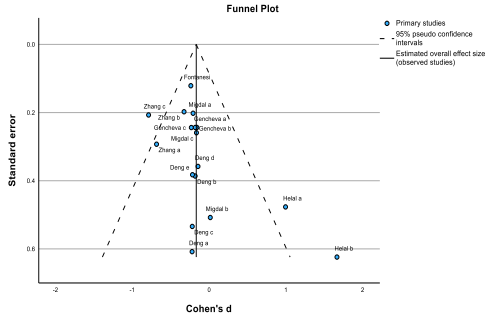
b. Co-dominant model (CC vs. GG)



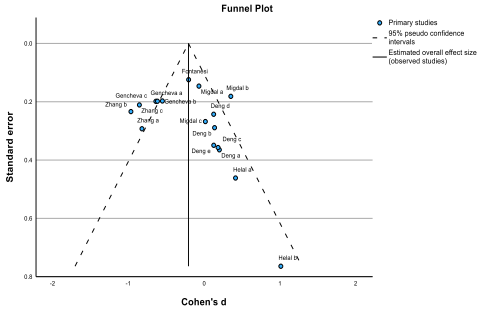
c. Co-dominant model (CG vs. GG)



d. Recessive model (CC vs CG+GG)



e. Dominant model (CC + CG vs GG)



f. Over-dominant model (CG vs CC + GG)

Figure 3. Funnel plot of standard error of the effect size for the meta-analysis of *GHR* gene association with rabbit body weight under various genetic models

In contrast, the funnel plots for the recessive and over-dominant genetic models were asymmetric, suggesting the presence of publication bias. The existence of publication bias suggests for some genetic models suggests that smaller studies reporting significant results may be overrepresented. However, Egger's regression test for the co-dominant (CC vs GG) and

dominant models was not significant (P > 0.05), and their funnel plots were symmetric, indicating an absence of publication bias under these models. The observed publication bias in some models could result from selective reporting of significant results, differences in study designs, or variations in sample sizes across studies.

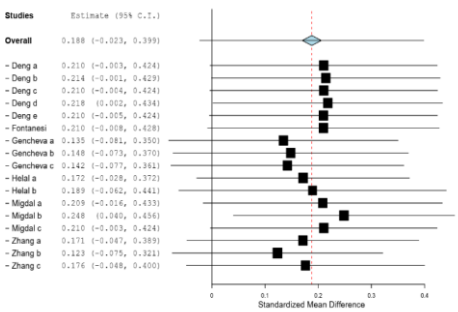
Sensitivity analysis of the association between GHR gene and body weight of rabbits

Figure 4 presents the sensitivity plots assessing the association between the *GHR* gene and body weight in rabbits under different genetic models. The sensitivity analysis revealed no substantial change in the overall effect size, as indicated by stable pooled standardized mean differences (SMDs) across the plots. This suggests that none of the individual studies exerted a disproportionate influence on the meta-analysis results, reinforcing the robustness and reliability of the findings.

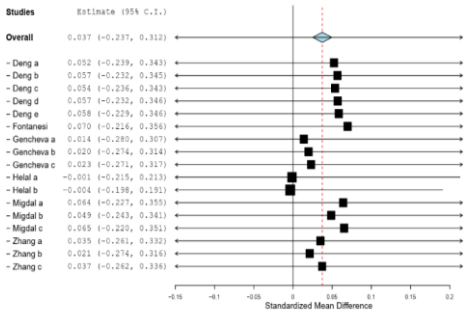
Meta-regression models for the association of GHR gene polymorphisms with body weight of rabbits

Table 6 presents the meta-regression model analyzing the association between *GHR* gene polymorphism and body weight of rabbits under co-dominant genetic models. For the CC vs CG and CC vs GG comparisons, the omnibus p-value was significant (P < 0.05), indicating that at least one of the covariates or moderators included in the meta-regression model had a significant effect on the overall effect size. Under both co-dominant genetic models, location, genotyping method, sample size, and breed had a significant effect (P < 0.05) on the overall effect size, while age of rabbits did not. However, for the CG vs GG genetic model, the omnibus p-value was not significant (P > 0.05), suggesting that none of the covariates or moderators included in the meta-regression model had a significant effect on the overall effect size. Specifically, location, genotyping method, sample size, age, and breed all had no significant effect (P > 0.05) on the overall effect size.

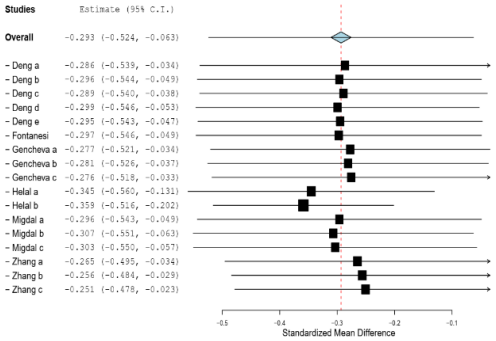
Table 7 presents the meta-regression model analyzing the association between *GHR* gene polymorphism and body weight of rabbits under the recessive, dominant, and over-dominant genetic models. For the recessive genetic model, the omnibus p-value was significant (P < 0.05), indicating that at least one of the covariates or moderators included in the meta-regression model had a significant effect on the overall effect size. Location, genotyping method, sample size, and breed had a significant effect (P < 0.05) on the overall effect size, while age of rabbits did not. However, for the dominant and over-dominant genetic models, the omnibus p-values were not significant (P > 0.05), suggesting that none of the covariates or moderators included in the meta-regression model had a significant effect on the overall effect size. Variations in the significance of meta-regression coefficients and moderators across different genetic models indicate that the relationship between *GHR* gene polymorphism and body weight is not uniform across all studies but varies depending on study characteristics. Furthermore, the non-significance of age across all models suggests that body weight differences associated with *GHR* polymorphism are not strongly dependent on the age at measurement. Overall, the results suggest that location, genotyping method, sample size, and breed should be carefully considered in future studies examining the effect of *GHR* gene polymorphism on body weight, as these factors could introduce variability and influence the detectability of genetic effects.



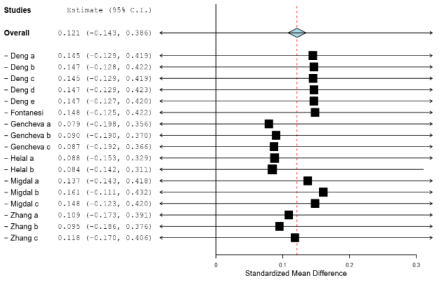
a. Co-dominant model (CC vs. CG)



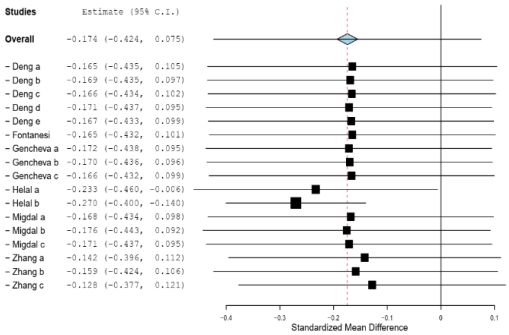
b. Co-dominant model (CC vs. GG)



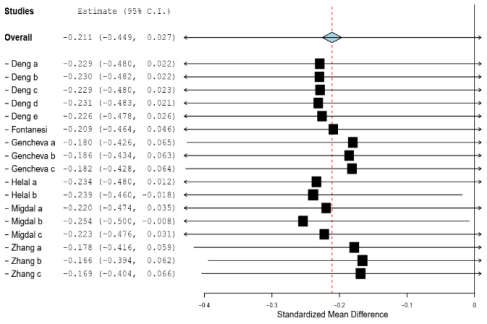
c. Co-dominant model (CG vs. GG)



d. Recessive model (CC vs CG+GG)



e. Dominant model (CC + CG vs GG)



f. Over-dominant model (CG vs CC + GG)

Figure 4. Sensitivity plot evaluating the influence of individual studies on the association between the *GHR* gene and body weight in rabbits under various genetic models

Table 6. Meta-regression model of the association of GHR gene with body weight of rabbits under the co-dominant genetic models

Covariate	Coefficients	Lower bound	Upper bound	SE	p-value
(CC vs CG) Omnibus p-value =0.024					
Intercept	4.805	2.244	7.366	1.307	< 0.001
Location	-0.476	-0.796	-0.157	0.163	0.003
Genotyping method	-2.002	-3.323	-0.681	0.674	0.003
Sample size	-0.006	-0.011	-0.001	0.002	0.015
Age	-0.005	-0.022	0.011	0.008	0.532
Breed	0.108	0.024	0.191	0.043	0.011
(CC vs GG) Omnibus p-value =0.018					
Intercept	3.758	1.598	5.919	1.102	< 0.001
Location	-0.319	-0.579	-0.059	0.133	0.016
Genotyping method	-1.783	-2.938	-0.628	0.589	0.002
Sample size	-0.007	-0.011	-0.003	0.002	< 0.001
Age	-0.002	-0.016	0.012	0.007	0.782
Breed	0.112	0.037	0.187	0.038	0.003
(CG vs GG) Omnibus p-value =0.115					
Intercept	-0.391	-2.278	1.496	0.963	0.684
Location	0.035	-0.185	0.256	0.112	0.754
Genotyping method	-0.268	-1.271	0.734	0.512	0.600
Sample size	0.000	-0.003	0.003	0.002	0.994
Age	0.006	-0.007	0.018	0.006	0.368
Breed	-0.021	-0.081	0.040	0.031	0.501

SE – Standard error

Table 7. Meta-regression model of the association of GHR gene with body weight of rabbits under the recessive, dominant and over-dominant genetic models

Covariate	Coefficients	Lower bound	Upper bound	SE	p-value
Recessive model (CC vs CG+GG) Omnibus p-value =0.005					
Intercept	4.530	2.397	6.662	1.088	< 0.001
Location	-0.423	-0.689	-0.156	0.136	0.002
Genotyping method	-1.973	-3.080	-0.867	0.565	< 0.001
Sample size	-0.006	-0.010	-0.002	0.002	0.002
Age	-0.004	-0.017	0.010	0.007	0.608
Breed	0.092	0.022	0.161	0.036	0.010
Dominant model (CC+CG vs GG) Omnibus p-value =0.083					
Intercept	1.162	-0.579	2.904	0.889	0.191
Location	-0.090	-0.294	0.115	0.105	0.391
Genotyping method	-0.873	-1.792	0.047	0.469	0.063
Sample size	-0.002	-0.005	0.000	0.001	0.078
Age	0.003	-0.009	0.015	0.006	0.602
Breed	0.018	-0.037	0.073	0.028	0.512

Over-dominant model (CG vs CC+GG) Omnibus p-value =0.157					
Intercept	-2.277	-4.555	-0.000	1.162	0.050
Location	0.248	-0.036	0.533	0.145	0.086
Genotyping method	0.672	-0.489	1.833	0.592	0.257
Sample size	0.001	-0.003	0.005	0.002	0.592
Age	0.008	-0.008	0.024	0.008	0.329
Breed	-0.052	-0.117	0.013	0.033	0.115

CONCLUSION

There was significant association of *GHR* gene with body weight of rabbit under the co-dominant model (CG vs GG). However, there were no significant association between polymorphisms in *GHR* gene and body weight under all other models. The findings from this study implied that the impact of *GHR* gene polymorphisms on body weight in rabbits may be influenced by specific genetic models. Furthermore, the observed higher body weight in rabbits with the GG genotype suggests a potential role of this genetic variant in promoting growth. However, further research is needed to explore the underlying mechanisms and confirm these associations.

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ETHICAL APPROVAL

No new human or animal subjects were involved in this study. This study does not raise any ethical concerns and ethical approval was not required.

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GENETSKI UTICAJ POLIMORFIZAMA RECEPTORA HORMONA RASTA (GHR) NA TELESNU TEŽINU ZEČEVA: META-ANALIZA

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Izvod

Regulacija rasta i metabolizma kod zečeva je pod uticajem receptora hormona rasta (GHR). Međutim, uprkos njegovom obećavajućem potencijalu kao kandidata za sekciju uz pomoć markera, veza između polimorfizama GHR gena i telesne težine pod različitim genetskim modelima ostaje neubedljiva. Ova studija je primenila sistematski pregled i meta-analizu kako bi procenila ovu vezu. Protokol je retrospektivno registrovan u okviru Open Science Framework-a. Prateći smernice Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA), analizirano je 17 tačaka podataka iz šest studija. Testiran je Hardi-Vajnbergov ekvilibrijum (HWE), a četiri genetska modela (ko-dominantni, dominantni, recesivni i prekomerno-dominantni) su prilagođena pomoću OpenMeta® Analyst softvera. Standardizovane srednje razlike (SMD) su procenjene korišćenjem Koenove d metode, sa heterogenošću procenjenom pomoću Q statistike, Tau-kvadrata (t^2), H-kvadrata (H^2) i I-kvadrata (I^2). Egerov regresioni test je korišćen za procenu pristrasnosti objavljivanja, a analiza osetljivosti je sprovedena da bi se utvrdili efekti pojedinačne studije. Postojala je značajna povezanost ($p<0,05$) GHR gena sa telesnom težinom zečeva pod jednim od kodominantnih modela (CG vs GG). Međutim, ova povezanost nije bila značajna ($p>0,05$) pod svim ostalim genetskim modelima. Dalje, rezultati su pokazali da je GG genotip imao veću telesnu težinu od CG genotipa. Međutim, nije bilo razlike ($p>0,05$) između CC i CG i CC i GG genotipova. Ovo ukazuje na to da polimorfizam GHR gena ima ograničen uticaj na telesnu težinu i da njihov uticaj može zavisiti od specifičnih genetskih modela.

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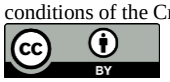

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