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Meta-analysis of association between Insulin-like growth factor-2 gene polymorphisms and growth traits in rabbits

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ABSTRACT: The Insulin-like growth factor-2 (*IGF-2*) gene is a potential candidate for marker assisted selection in rabbits due to its crucial role in regulating growth. However, the relationship between polymorphic variants of this gene and growth performance traits of rabbits under different genetic models has not been established. Therefore, the objective of this study was to assess the association between *IGF-2* gene polymorphisms and growth performance traits in rabbits using meta-analysis. A systematic review was conducted following the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guideline to identify and select relevant studies for inclusion in the analysis. Data were extracted from nine reports and included in the final analysis. Six genetic models under the assumption of co-dominance (3 models), recessive (1 model), dominance (1 model) and over-dominance (1 model) were evaluated. SPSS software was used for the assessment of heterogeneity, effect size calculation using Hedges' g method for standardized mean differences (SMDs) and the assessment of publication bias, while sensitivity analysis was conducted using OpenMeta® Analyst software. High heterogeneity was observed across studies under all genetic models. In addition, there were significant associations ($P<0.05$) between of *IGF-2* gene with growth performance traits of rabbits. A simple relationship between these genotypes for growth traits of rabbits could be stated as Del/Del > A/Del >A/A. Rabbits carrying the Del/Del genotype consistently exhibited higher body weight and growth rate, followed by heterozygotes (A/Del), while those with the AA genotype showed the lowest growth performance. The findings infer the superiority of the Del allele over the A allele (Del>A) for growth performance traits of rabbits. These findings implied that the *IGF-2* gene could be a potential candidate gene for marker assisted selection of rabbits for improved growth performance.

Keyword: Insulin-like Growth Factor-2; Meta-analysis; Gene polymorphism; Rabbits; Marker assisted selection

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INTRODUCTION

According to Hatab et al. (2019), the livestock sector contributes significantly to food security by supplying animal protein globally. It also provides livelihood opportunities especially in low- and middle-income countries (Michalk et al., 2018). However, despite its significance, the sector faces challenges related to low productivity especially among indigenous and locally adapted breeds in developing countries (McDermott et al., 2010; Kpomasse et al., 2023). Selective breeding through marker assisted selection for improved growth performance has been suggested as a key strategy for improving livestock productivity (Olaniyan et al., 2024). Furthermore, the identification and characterization of genetic polymorphisms associated with economically important traits in livestock species have gained significant attention in recent times (Zalewska et al., 2021; Ateya et al., 2022; Huang et al., 2023; Magotra et al., 2023; Ayele et al., 2024; Pauciullo et al., 2024).

One such candidate gene with potential application for marker assisted selection for growth performance in livestock is the Insulin-like Growth Factor-2 (*IGF-2*) gene. The roles of *IGF-2* in the regulation of pre- and post-natal growth through mechanism of cell proliferation, differentiation, and metabolism in multiple tissue types have been established (Chao and D'Amore, 2008; Harris and Westwood, 2011; Torrente et al., 2020; LeRoith et al., 2021). Therefore, polymorphisms within the *IGF-2* encoding gene have been widely investigated for their association with growth-related traits in pigs (Huang et al., 2012; Li et al., 2012; Ampaporn et al., 2023), cattle (Zhang and Li, 2008; Berkowicz et al., 2010; Huang et al., 2013), poultry (Wang et al., 2005; Hosnedlová et al., 2020; Nurcahya et al., 2020; Wu et al., 2025) and rabbits (Fontanesi et al., 2012; Abdel-Kafy et al., 2014; Ramadan et al., 2020; Safaa et al., 2023).

Rabbits are recognized as an important livestock species, with significant contributions to food security especially in developing countries. They are particularly cherished for their rapid growth rate, high feed conversion efficiency, and lean meat production (Cullere and Zotte, 2018). In order to improve the growth performance traits of rabbits, the genetic basis of growth have been explored through candidate gene association studies with the *IGF-2* gene polymorphisms. However, findings remain inconsistent. Some authors reported significant associations with body weight and growth rate, while others find no association. For instance, Abdel-Kafy et al. (2014) found no significant differences in body weight among AA, A/Del, and Del/Del genotypes of APRI rabbits at 5, 6, and 8 weeks but observed significantly higher body weight in Del/Del variants at 10 and 12 weeks. Similarly, Fontanesi et al. (2012) and Ramadan et al. (2020) reported that Del/Del rabbits had the highest finishing weight. Meta-analysis can help clarify the true effect of *IGF-2* polymorphisms on rabbit growth performance traits by increasing statistical power and minimizing biases inherent in individual studies. Therefore, the objective of this study was to conduct a meta-analysis of existing research on the association between *IGF-2* gene polymorphisms and growth performance traits in rabbits.

MATERIALS AND METHODS

Search strategy

This study was retrospectively registered on the Open Science Framework (OSF) under registration DOI [https://doi.org/10.17605/OSF.IO/E8HC9]. This contains the full protocol, including the search strategy, inclusion criteria, and analysis plan. We conducted a comprehensive database search for articles following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline (Moher et al., 2009). We used several keywords and terms in the electronic database search, including SNP, insulin-like growth factor-2, association, polymorphism, gene, *IGF-2*, rabbit, growth performance, body weight, average daily gain, and growth traits. We combined these terms into search phrases such as "association of insulin-like growth factor (*IGF-2*) gene with body weight and average daily gain of rabbits" and "*IGF-2* gene in rabbits," among others.

Eligibility Criteria

We established pre-determined eligibility criteria to determine whether a study should be included in the analysis. The PICO (Population, Intervention, Comparison, Outcome) framework guided the development of these criteria. We included studies that met the following criteria: they were original research rather than review articles or summaries, reported polymorphisms in the *IGF-2* gene of rabbits, and examined the effects of *IGF-2* on growth traits such as body weight (BW) or average daily gain (ADG). Additionally, studies had to provide sample size details, including the number of rabbits per genotype or genotype ratio, as well as least squares

means for growth traits. Furthermore, they needed to report either standard deviations or standard errors for each least squares mean estimate.

Study Selection

Figure 1 summarizes the study selection process. Initially, 128 published articles were retrieved from databases using the search strategy. After removing duplicates, 106 studies remained. The titles and abstracts of these studies were screened, leading to the selection of 21 relevant articles for full-text assessment based on pre-determined eligibility criteria. Ultimately, data points were extracted from nine reports for the final analysis. These studies were published between 2011 and 2020.

Data Extraction

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, country of study, sample size, genotype number, mean body weight, average daily gain, standard deviation, standard error, and significance level. After extraction, the data were reviewed and reconciled to ensure consistency and accuracy.

Data analysis

The gene calculator software freely available online: https://wpcalc.com/en/equilibrium-hardy-weinberg/ was used to subject each study to Hardy-Weinberg Equilibrium (HWE) test. Meta-analysis was conducted using the Metafor package in R (Viechtbauer, 2010; R, 2022), SPSS (SPSS, 2021), and OpenMeta Analyst (Wallace et al., 2012). Six genetic models were applied to assess the association between the *IGF-2* gene and growth traits (body weight and average daily gain) in rabbits. These models included three co-dominant models, one recessive model, one dominant model, and one over-dominant model, as summarized in Table 1.

SPSS (2021) software was used to calculate standardized mean differences (SMDs) to estimate both individual study effect sizes and the overall effect size. Heterogeneity was assessed using the Q statistic (Chi-square test) and its associated p-value, along with Tau-squared (T^2), H-squared (H^2), and I-squared (I^2) values using SPSS. Due to high heterogeneity, a random-effects model was applied. To visualize individual study effect sizes, standard errors, confidence intervals, and the overall effect size, Forest plots were generated. Publication bias was evaluated through both visual inspection of funnel plots and

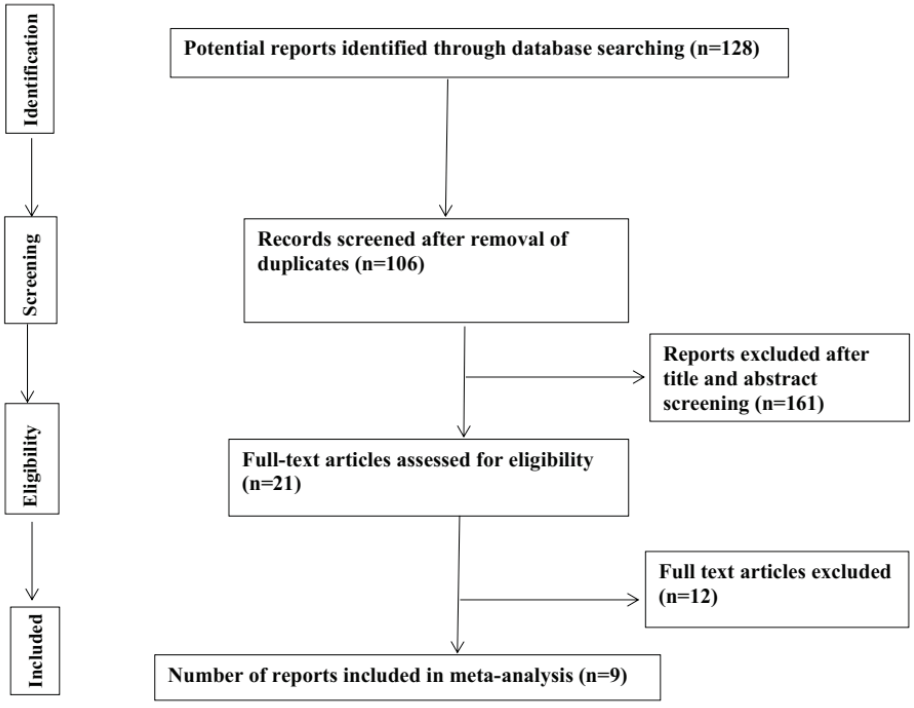


Figure 1. PRISMA flow diagram for study selection in the meta-analysis of *IGF-2* gene polymorphism and growth traits in rabbits.

Table 1. Genetic models fitted for meta-analyses of association of *IGF-2* gene polymorphism and growth traits in rabbits

Category	Specific genetic model
Co-dominant	AA vs A/Del
Co-dominant	AA vs Del/Del
Co-dominant	A/Del vs Del/Del
Recessive	AA vs A/Del+Del/Del
Dominant	AA+A/Del vs Del/Del
Over-dominant	A/Del vs AA+Del/Del

Egger's regression asymmetry test. Additionally, a sensitivity analysis was performed using the Metafor package in R via OpenMeta Analyst (Wallace et al., 2012) to determine whether a single study had a disproportionate influence on the overall effect size.

RESULTS

Summary of reports included in the meta-analysis

Table 2 presents a summary of the studies included in the meta-analysis of the association between polymorphisms in the IGF-2 gene and growth traits in rabbits. A total of nine reports were identified. The studies were conducted from 2011 to 2020 in Egypt and Italy. Studies by Ramadan et al. (2020) and Abdel-Kafy et al. (2014) generated multiple data points at different ages, which allows for age-specific meta-analyses of gene–trait associations. Specifically, the Egyptian studies focused on Gabali and APRI breeds, both of which are meat-type rabbits with potential for commercial production under arid and semi-arid conditions. Furthermore, Fontanesi et al. (2012) utilized different meat-type rabbit breeds and lines including Californian, Champagne d'Argent, Checkered Giant, Chinchilla, Giant Grey, New Zealand White, Loop and Vienna Blue. The inclusion of different breeds ensures some genetic heterogeneity, which is crucial for robust inference in association studies. All studies used the PCR-RFLP technique which ensured consistency in genotyping protocols across datasets. This methodological uniformity also reduces the risk of technical heterogeneity that could bias the meta-analytic outcomes. Across reports, phenotypic data were recorded at various ages ranging from 28 to 84 days. This provides a temporal dimension to evaluate the dynamic influence of the *IGF-2* gene on growth traits during early to mid-growth stages of meat rabbits.

Hardy-Weinberg equilibrium assessment of studies included in the meta-analysis

Table 3 presents the Hardy-Weinberg equilibrium (HWE) status of studies evaluated and included for the meta-analysis of association between *IGF-2* gene polymorphisms and growth traits of rabbits. All studies included reported gene polymorphism in c.156+61delA indel in rabbits. The HWE test was conducted to determine whether the observed genotype frequencies in each study population deviated significantly from the expected frequencies. To account for multiple testing and control the false discovery rate, the Hardy-Weinberg p values were adjusted using the Benjamini-Hochberg procedure. After this adjustment, all the included studies had p values greater than 0.05. This indicated that none showed significant deviation from HWE. If significant deviations from HWE were observed, it would indicate a potential issue that might affect the genetic distribution within the sample population (Minelli et al., 2007). Depending on the reason for the deviation,

Table 2. Summary of reports included in the meta-analysis of association between polymorphisms in *IGF-2* gene and growth traits of rabbits

Report	Location	Breed	Type	Year	Genotyping method	Age (days)
Ramadan a	Egypt	Gabali	Meat	2020	PCR-RFLP	28
Ramadan b	Egypt	Gabali	Meat	2020	PCR-RFLP	56
Ramadan c	Egypt	Gabali	Meat	2020	PCR-RFLP	84
Fontanesi	Italy	Multiple breeds	Meat	2012	PCR-RFLP	70
Abdel-Kafy a	Egypt	APRI	Meat	2014	PCR-RFLP	35
Abdel-Kafy b	Egypt	APRI	Meat	2014	PCR-RFLP	42
Abdel-Kafy c	Egypt	APRI	Meat	2014	PCR-RFLP	56
Abdel-Kafy d	Egypt	APRI	Meat	2014	PCR-RFLP	70
Abdel-Kafy e	Egypt	APRI	Meat	2014	PCR-RFLP	84

Table 3. Assessment of Hardy-Weinberg equilibrium in studies included in the meta-analysis of association of *IGF-2* genes with growth traits of rabbits

Reports	HW Chi-square value	HW p value	Benjamini-Hochberg Adjusted HW p value
Ramadan et al. a	2.3603	0.3072	0.9217
Ramadan et al. b	2.1362	0.4076	0.8722
Ramadan et al. c	1.8922	0.5111	0.9146
Abdel-Kafy et al. a	0.7599	0.6839	1.000
Abdel-Kafy et al. b	1.2310	0.5027	1.000
Abdel-Kafy et al. c	0.6578	0.7271	1.000
Abdel-Kafy et al. d	0.6678	0.8243	1.000
Abdel-Kafy et al. e	2.4117	0.3452	1.000
Fontanesi et al.	0.5804	0.7481	0.7481

*HW: Hardy-Weinberg

such study could be excluded from the meta-analysis to maintain the accuracy and robustness of the pooled results (Thakkinstian et al., 2005). However, the decision to exclude a study usually depends on whether it is likely to influence the overall results of the meta-analysis (Attia et al., 2003).

Heterogeneity genetic models for the meta-analysis of the association between *IGF-2* gene and growth performance traits of rabbits

Table 4 presents the heterogeneity test of six genetic models for the meta-analysis of the association between *IGF-2* gene and growth traits of rabbits. The measures of heterogeneity included the τ^2, H^2, I^2 and the Q- statistic. τ^2 (Tau-squared) represents the variance of true effect sizes across studies in the meta-analysis and it indicated the absolute amount of heterogeneity (Hamad and Alkhawaldeh, 2024) while H^2 (H-squared) measures the total variability relative to sampling variability (Borenstein, 2023a). H^2 values greater than 1 suggest the presence of heterogeneity beyond chance while I^2 (I-squared) expresses the proportion of total variability due to true heterogeneity rather than random error (Borenstein, 2023b). I^2 typically ranges from 0% (no heterogeneity) to 100% (substantial heterogeneity) (Huedo-Medina et al., 2006).

For body weight and average daily weight gain, the Chi-square test for all genetic models were significant ($P<0.05$). Furthermore, the I^2 values were high for all genetic models fitted (I^2 >63%, ranged from 63.4% to 92.0%) and were thus considered heterogeneous. The heterogeneity test is a measure of how the effect size varies from one study to another and to assess if the overall effect size is in conformity with normal distribution. Thus, high heterogeneity measures obtained under all genetic models fitted indicated that effect size reported by different studies were due to systematic differences and not solely due to sampling error between studies included in the meta-analysis.

Effect size estimates of genetic models for *IGF-2* and growth traits in rabbits

Table 5 presents the overall effect size estimates of the six genetic models for the meta-analysis of the association between *IGF-2* gene and growth traits in rabbits. For body weight, the overall effect size under different genetic models fitted ranged from -0.613 (co-dominant -AA vs Del/Del) to -0.158 (over-dominant model). There were significant associations ($P<0.05$) of *IGF-2* gene with body weight of rabbits under all genetic models evaluated. The negative significant overall effect size under the co-dominant (AA vs A/Del) indicated that, when all studies included in the meta-analysis of association between *IGF-2* gene and body weight of rabbits were pooled, the body weight of rabbits with A/Del genotype was higher ($P<0.05$) than the body weight rabbit of AA genotype. Similar trends were also observed under the other co-dominant models (AA vs Del/Del and A/Del vs Del/Del) where rabbits with Del/Del genotype had higher body weight compared to rabbits with AA and A/Del genotypes, respectively. Thus, a simple relationship between these genotypes could be stated as Del/Del > A/Del >AA. This could infer the superiority of the Del allele over the A allele (Del>A) for body weight of rabbits. Furthermore,

Table 4. Heterogeneity test of six genetic models for the meta-analysis of the association between *IGF-2* gene and growth traits of rabbits

Category	Genetic model	τ^2	H^2	I^2	Chi-square (Q statistic)	P value
Body weight (BW)						
Co-dominant	AA vs A/Del	0.075	3.666	72.7	27.764	<0.001
Co-dominant	AA vs Del/Del	0.381	12.534	92.0	87.552	<0.001
Co-dominant	A/Del vs Del/Del	0.075	5.150	80.6	39.651	<0.001
Recessive	AA vs A/Del+Del/Del	0.155	7.212	86.1	55.053	<0.001
Dominant	AA+A/Del vs Del/Del	0.128	9.083	89.0	69.266	<0.001
Over-dominant	A/Del vs AA+Del/Del	0.020	3.155	63.4	9.320	0.0316
Average daily weight gain (ADG)						
Co-dominant	AA vs A/Del	0.086	3.803	73.7	18.926	0.002
Co-dominant	AA vs Del/Del	0.290	9.821	89.8	49.875	<0.001
Co-dominant	A/Del vs Del/Del	0.040	3.310	69.8	16.480	0.006
Recessive	AA vs A/Del+Del/Del	0.145	6.375	84.3	31.822	<0.001
Dominant	AA+A/Del vs Del/Del	0.082	6.428	84.4	31.498	<0.001
Over-dominant	A/Del vs AA+Del/Del	0.096	3.516	72.5	14.684	<0.001

τ^2=Tau-squared; H^2 =H-squared; I^2=I-squared
† :τ^2 (Tau-squared): Represents the variance of true effect sizes across studies in a meta-analysis.
† † : H^2 (H-squared): Measures the total variability relative to sampling variability.
* : I^2 (I-squared): Expresses the proportion of total variability due to true heterogeneity rather than random error.

Table 5. Overall effect size estimates of the six genetic models for the meta-analysis of the association between *IGF-2* gene and body weight of rabbits

Category	Genetic model	Effect size (SMD ± SE)	95% CI	95% PI	P value
Body weight (BW)					
Co-dominant	AA vs A/Del	-0.238±0.1075	-0.449 to 0.027	-0.934 to 0.458	0.027
Co-dominant	AA vs Del/Del	-0.613±0.2144	-1.033 to 0.192	-2.157 to 0.932	0.004
Co-dominant	A/Del vs Del/Del	-0.36±0.1016	-0.562 to 0.164	-1.052 to 0.326	<0.001
Recessive	AA vs A/Del+Del/Del	-0.38±0.1415	-0.666 to 0.112	-1.377 to 0.599	0.006
Dominant	AA+A/Del vs Del/Del	-0.420±0.1268	-0.669 to 0.172	-1.319 to 0.479	<0.001
Over-dominant	A/Del vs AA+Del/Del	-0.158±0.0427	-0.242 to 0.074	-0.308 to-0.008	<0.001
Average daily weight gain (ADG)					
Co-dominant	AA vs A/Del	-0.217±0.1395	-0.490 to 0.057	-1.119 to 0.685	0.120
Co-dominant	AA vs Del/Del	-0.586±0.2322	-1.041 to -1.131	-2.215 to 1.043	0.012
Co-dominant	A/Del vs Del/Del	-0.361±0.0972	-0.552 to -0.171	-0.976 to 0.253	<0.001
Recessive	AA vs A/Del+Del/Del	-0.378±0.1693	-0.710 to-0.046	-1.535 to 0.779	0.026
Dominant	AA+A/Del vs Del/Del	-0.412±0.1270	-0.661 to -0.163	-1.281 to 0.457	0.001
Over-dominant	A/Del vs AA+Del/Del	-0.182±0.0489	-0.278 to -0.086	-0.318 to -0.047	<0.001

*SMD: Standardized Mean difference
**SE: Standard error
†CI: Confidence interval
†† PI: Prediction interval

under the recessive model (AA vs A/Del+Del/Del), the overall effect size was significant and negative which indicated that an average of the A/Del + Del/Del genotypes had superior body weight compared to the AA genotype. In particular, the Del/Del genotype was the best genotype as shown in the dominant model (AA+A/Del vs Del/Del) with significant and negative overall effect size which showed that Del/Del genotype outperformed average of AA and A/Del genotypes in terms of body weight. Furthermore, under the over-dominant model, an average of AA and Del/Del genotypes had lower body weight compared with the A/Del genotype as shown by the significant but negative overall effect size.

For average daily weight gain of rabbits, the overall effect size under different genetic models fitted ranged from -0.586 (co-dominant -AA vs Del/Del) to -0.182 (over-dominant model). There was no significant association between *IGF-2* gene polymorphism and average daily weight gain of rabbit under the co-dominant model (AA vs A/Del). However, there were significant associations (P<0.05) of *IGF-2* gene polymorphisms with ADG of rabbits under other genetic models. The overall effect size was not significant (P>0.05) under the co-dominant model (AA vs A/Del) indicating that, when studies were pooled together by meta-analysis, there was no significant difference in the ADG between AA and A/Del genotypes. However, under other co-dominant models (AA vs Del/Del and A/Del vs Del/Del), the overall effect sizes were significant and negative indicating that the Del/Del genotypes outperformed the AA and A/Del genotypes, respectively. Furthermore, under the recessive (AA vs A/Del+Del/Del) and dominant (AA+A/Del vs Del/Del) genetic models, the effect sizes were negative and significant (P<0.05), showing that an average of A/Del and Del/Del genotype and Del/Del genotype had higher significant ADG compared with AA and an average of AA and A/Del genotype, respectively. Similarly, the Del/Del genotype had higher ADG than an average of AA and A/Del genotype when all studies were pooled together as indicated by negative and significant overall effect size under the over-dominant (AA+A/Del vs Del/Del) genetic model.

Publication bias

Egger's regression test for the assessment of publication bias

Table 6 presents the Egger's regression test for six genetic models for the assessment of publication bias for the random effects meta-analysis of association between *IGF-2* gene and growth traits of rabbits. For body weight, the Egger's regression-based tests were not significant (P>0.05) under all six genetic models evaluated suggesting that the number of studies utilized for the meta-analysis were adequate. Furthermore, there were no theoretically missing study under any of the genetic models which indicated that there was no publication bias in the assessment of association between *IGF-2* gene and body weight of rabbits. However, for the meta-analysis of association between *IGF-2* gene and average daily weight gain of rabbits, the Egger's regression tests were significant (P<0.05) under the co-dominant (AA vs A/Del) model, and recessive model. Furthermore, the tests predicted one theoretical missing study for the analysis under these two genetic models and thus suggest the existence of publication bias under these models.

Funnel plots for the assessment of publication bias

The funnel plot of the standard error of effect size for the meta-analysis of association between *IGF-2* gene, body weight and average daily weight gain of rabbits under different genetic models are presented in Figures 2 and 3, respectively. For body weight, the funnel plots under all genetic models were symmetric with most of the studies located within the 95% of the confidence interval of the effect size indicating that there was no publication bias or small-study effects in the meta-analysis of the association between *IGF-2* gene and body weight of rabbits. However, for average daily weight gain, the funnel plots were asymmetric under the co-dominant model (AA vs A/Del) and recessive model suggesting that there was publication bias or small-study effects under these models. Conversely, the funnel plots were symmetric under the dominant and over-dominant models which indicated that there was no publication bias or small-study effects under these models.

Sensitivity analysis of association *IGF-2* gene and growth traits

Figure 4 presents the sensitivity plots of the association between *IGF-2* gene and body weight of rabbits under various genetic models. The plots showed no significant difference in the overall effect size (pooled SMDs) indicating that none of the single studies was responsible for the overall results.

DISCUSSION

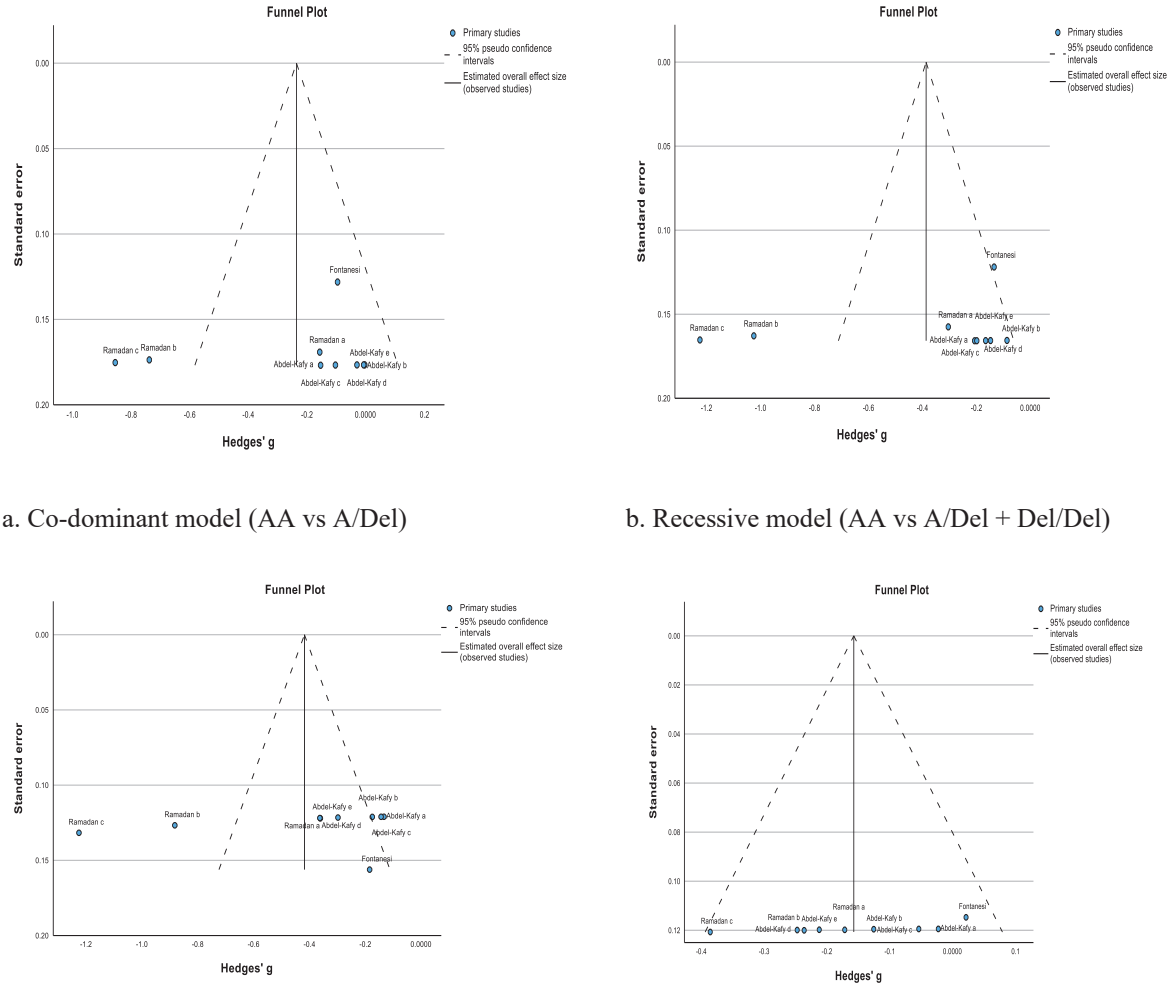
In the present study, significant associations between the *IGF-2* gene and growth performance traits were observed under multiple genetic models. Further,

Table 6. Egger's regression test for six genetic models for the assessment of publication bias for the random effects meta-analysis of association between *IGF-2* gene and growth traits of rabbits

Category	Genetic model	Regression coefficient ± SE	95% CI	p-value	Number of missing studies
Body weight (BW)					
Co-dominant	AA vs A/Del	0.214±1.2259	-2.685 to 3.112	0.867	0
Co-dominant	AA vs Del/Del	0.993±0.7136	-0.468 to 3.518	0.138	0
Co-dominant	A/Del vs Del/Del	-0.279±1.4187	-3.634 to 3.076	0.850	0
Recessive	AA vs A/Del+Del/Del	0.550±1.7026	-3.476 to 4.576	0.756	0
Dominant	AA+A/Del vs Del/Del	-0.024±0.619	-2.853 to 2.804	0.881	0
Over-dominant	A/Del vs AA+Del/Del	5.785±2.7899	-0.812 to 12.382	0.077	0
Average daily weight gain (ADG)					
Co-dominant	AA vs A/Del	-6.453±2.357	-9.209 to 7.302	0.0467	1
Co-dominant	AA vs Del/Del	14.786±4.837	1.356 to 28.216	0.083	0
Co-dominant	A/Del vs Del/Del	13.978±3.753	3.559 to 24.397	0.2013	0
Recessive	AA vs A/Del+Del/Del	-10.737±2.123	-17.868 to 14.39	0.0251	1
Dominant	AA+A/Del vs Del/Del	6.013±4.0073	2.664 to 24.362	0.7643	0
Over-dominant	A/Del vs AA+Del/Del	41.961±20.376	-14.612 to 98.53	0.109	0

*SE- Standard error
**CI- Confidence interval

the Del/Del genotype and Del allele was associated with higher body weight and average daily weight gain of rabbits. The superior performance of the Del/Del genotype may be attributed to differences in transcriptional activity or mRNA stability conferred by the deletion mutation. In pigs, a similar polymorphism in the *IGF-2* gene is known to affect intron methylation patterns and binding of transcriptional repressors leading to increased gene expression and muscle growth (Laere et al., 2003), intramuscular fat (Aslan et al., 2011) and fatty acid composition of the adipose tissue (Criado-Mesas et al., 2019). In cattle, *IGF-2* polymorphisms have been demonstrated to alter promoter activity and epigenetic regulation to influence fetal growth and postnatal muscle development (Long and Cai, 2007). In chickens, *IGF-2* gene polymorphisms impact transcription factor binding sites, leading to differential gene expression associated with body weight and muscle deposition (Li et al., 2006; Xue et al., 2017). It is plausible that a comparable mechanism operates in rabbits, with the Del allele enhancing *IGF-2* expression, thus stimulating growth-promoting processes such as myogenesis, cell proliferation, and nutrient utilization. This aligns with the findings of Fontanesi et al. (2012) that reported a significant association (P<0.05) between *IGF-2* polymorphism and finishing weight in rabbits, with the Del/Del genotype exhibiting the heaviest finishing weight, followed by A/Del, while the AA genotype had the lowest. Furthermore, Ramadan et al. (2020) also reported that Sinai Gabali rabbits in Egypt carrying the Del/Del genotype had significantly higher (P<0.05) body weight at 4, 8, and 12 weeks of age compared to A/Del and AA genotypes. However, Abdel-Kafy et al. (2014) reported no significant differences (P>0.05) in body weight among AA, A/Del, and Del/Del genotypes of APRI rabbits at 5, 6, and 8 weeks of age but found that the Del/Del genotype had significantly higher (P<0.05) body weight at 10 and 12 weeks of age. Additionally, Abdel-Kafy et al. (2014) also reported that *IGF-2* polymorphisms significantly (P<0.05) influenced the weight of edible giblets, fore-quarter, and loin, while no significant association was found for hind-quarter weight. At the allelic level, the strong associations observed in this meta-analysis, particularly under co-dominant and dominant genetic models, suggest that the Del allele is advantageous for growth traits. The implication of this is that the deletion of the A allele in the *IGF-2* gene confers superior growth performance and could possibly serve as valuable genetic markers for marker-assisted selection (MAS) aimed at improving rabbit growth performance. These results are consistent with studies in other livestock species. For example, Bagnicka et al. (2009) and Berkowicz



a. Co-dominant model (AA vs A/Del)

b. Recessive model (AA vs A/Del + Del/Del)

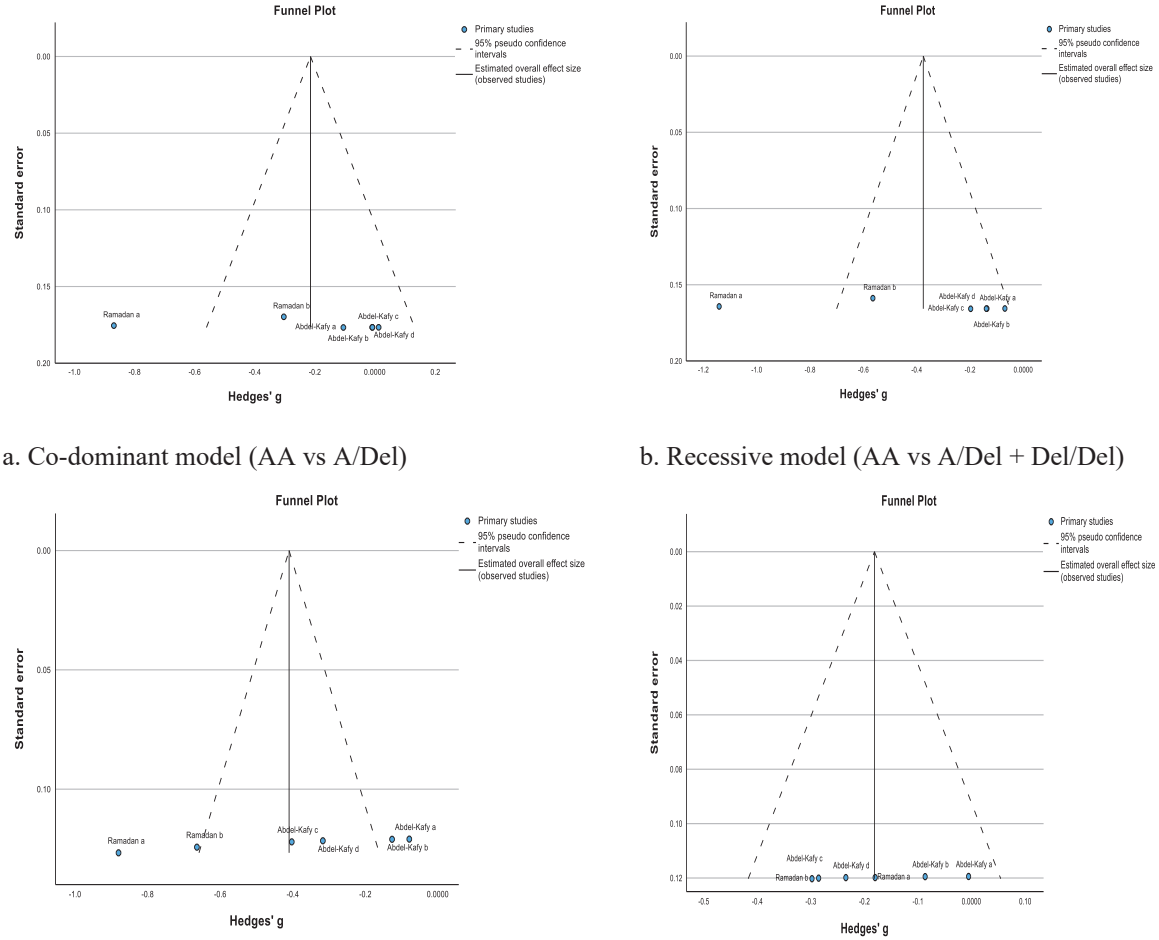
c. Dominant model (AA + A/Del vs Del/Del)

d. Over-dominant model (A/Del vs AA + Del/Del)

Figure 2. Funnel plot of the standard error of effect size for the meta-analysis of association between *IGF-2* gene and body weight of rabbits.

et al. (2010) found that polymorphisms at the *IGF-2* locus significantly influenced dairy performance in Polish and Irish Holstein- Friesian cattle, respectively. Further, Hosnedlová et al. (2020) observed associations between *IGF* family gene variants and growth traits in broiler chickens. In pigs, a well-known G3072A polymorphism in *IGF-2* is linked to increased muscle depth and decreased backfat thickness (Huang et al., 2012). These similarities suggest that the *IGF-2* gene may play a conserved role in regulating growth traits across mammalian and avian livestock.

High heterogeneity was noted across all genetic models, suggesting that factors such as genetic background, breed differences, and environmental influences contributed to the observed variations. Breed-specific effects have been reported in previous studies, with certain rabbit breeds responding differently to *IGF-2* polymorphisms due to differences in genetic architecture and selection pressures (Helal et al., 2021; Safaa et al., 2023). Additionally, environmental factors such as nutrition and management practices may have influenced growth performance, contributing to the variability observed across studies. Publication bias was generally low, as indicated by non-significance of Egger's regression test and the symmetry of the funnel plots. However, some bias was detected in the assessment of average daily gain under the co-dominant (AA vs. A/Del) and recessive models, suggesting the need for additional studies to strengthen the evidence for the association of *IGF-2* polymorphisms with ADG. Therefore, as



a. Co-dominant model (AA vs A/Del)

b. Recessive model (AA vs A/Del + Del/Del)

c. Dominant model (AA + A/Del vs Del/Del)

d. Over-dominant model (A/Del vs AA + Del/Del)

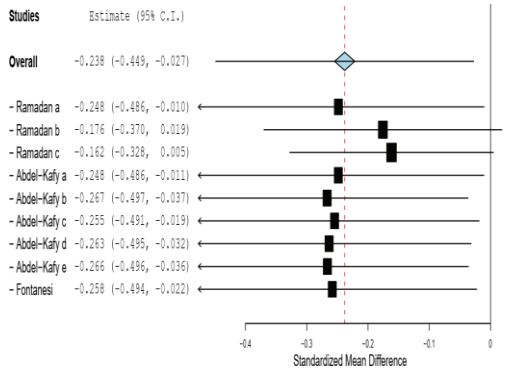
Figure 3. Funnel plot of the standard error of effect size for the meta-analysis of association between *IGF-2* gene and average daily weight gain of rabbits.

new research emerges, an updated meta-analysis will be necessary to validate the associations reported in this study and refine the implications of *IGF-2* gene polymorphisms for genetic selection in rabbit breeding programs.

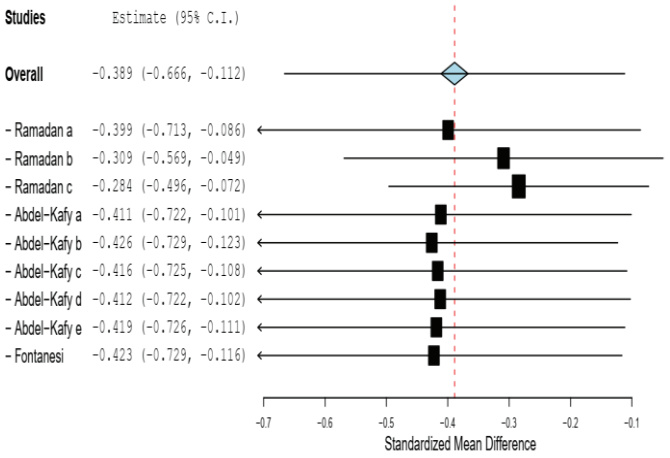
A limitation of this meta-analysis is the small number of studies included, which may limit the generalizability of the findings. Additionally, variations in phenotyping accuracy across studies may contribute to unexplained variability. Furthermore, it is important to acknowledge that growth performance in rabbits, like in most livestock species, is a complex quantitative trait influenced by the combined action of multiple genes. While the findings of this meta-analysis highlight a significant association between *IGF-2* polymorphisms and growth traits, it is likely that *IGF-2* accounts for only a small proportion of the total genetic variance underlying these traits. The observed effect sizes, although statistically significant in several genetic models, suggest a modest contribution of *IGF-2* to overall growth performance. Therefore, while *IGF-2* may serve as a useful marker in selection programs, its integration should be complemented with information from other growth-related candidate genes and genomic regions to achieve a sustainable genetic improvement for rabbits.

CONCLUSIONS

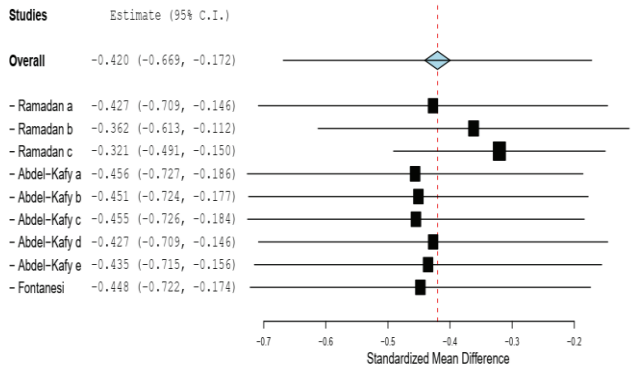
In conclusion, single nucleotide polymorphisms in *IGF-2* gene are significantly associated with the body weight of rabbits across various genetic models. The Del/Del genotype had the highest body weight followed by A/Del and A/A genotypes. This



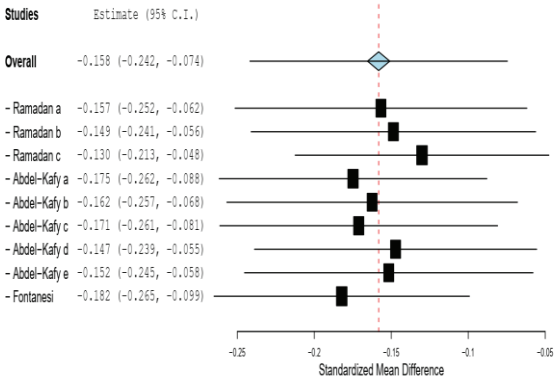
a. Co-dominant model (AA vs A/Del)



b. Recessive model (AA vs A/Del + Del/Del)



c. Dominant model (AA + A/Del vs Del/Del)



d. Over-dominant model (A/Del vs AA + Del/Del)

Figure 4. Sensitivity plot of the association between *IGF-2* gene and body weight of rabbits.

suggests that the presence of the Del allele confers a body weight advantage over the A allele. These findings implied that the *IGF-2* could be a potential candidate gene for marker assisted selection of rabbits for improved growth performance.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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