Iranian Society of Animal Science

Journal of Livestock Science and Technologies

Shahid Bahonar University of Kerman

ISSN: 2322-3553 (Print) ISSN: 2322-374X (Online)

Paper type: Original Research

A meta-analysis study of the association between FecB polymorphism and litter size in sheep

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Received: 03 Jul 2022,
Accepted: 12 Aug 2022,
Published online: 05 Dec 2022,

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Abstract In the current study, a meta-analysis was carried out by merging outcomes resulting from 26 published studies in various breeds of sheep to assess the influence of the FecB gene on litter size by applying the additive, recessive, dominant, and co-dominant genetic models. The model with random effects was used for data analysis according to the Cochran Q test and I^2 quantity statistical measures. Standardized mean difference (SMD) was applied to measure the size effects of '+' and B alleles of FecB on the litter size. The significant effect (P<0.01) of FecB genotypes on the litter size was identified under the additive (SMD = 0.511), dominant (SMD = 0.469) and recessive (SMD = 0.255) models. An increase in the litter size by approximately 0.47 lambs (Dominant model) was associated with the first copy of the FecB gene and 0.25 lambs (Recessive model) with the second copy of FecB. The findings of the current study supported the idea that BMPR1B would fundamentally influence the litter size in sheep. Subsequently, it may be utilized in marker-assisted selection programs to improve the genetic merit of litter size in the future. Introgression this gene through crossbreeding programs in low prolific breeds may improve reproductive performance.

Keywords: association studies, fecundity genes, marker-assisted selection, Ovis *aries*, reproduction traits

Introduction

Traditional sheep production systems are not cost-effective and sustainable mainly due to the low efficiency followed by climate change. One of the most well-known and appropriate methods for improving production efficiency is to improve the fecundity and fertility of the flocks via selective breeding (Li et al., 2021). Litter size is one of the important reproductive traits in sheep, which is affected by genetic and environmental factors. Because of the low heritability of this trait, the traditional breeding strategies have been ineffective for improving the trait rapidly (Mahdavi et al., 2014; Wang et al., 2015). Consequently, the researchers sought to seek several variants of the candidate genes that influence the litter size, which should stand helpful for marker-assisted selection and molecular genetics techniques. A range of different genes, commonly known as fecundity (Fec) genes, affect the litter size. One of the most famous genes is Bone Morphogenetic Protein Receptor Type 1B (BMPR1B), which is renowned as the Activin-like Kinase 6 or FecB or Booroola gene (Wilson et al., 2001; Chu et al., 2011; Plakkot et al., 2020; Sharma et al., 2022).

The Booroola gene is a member of the Transforming

Growth Factor (TGF) β super-family; which is mapped at the FecB locus existing among the Osteopontin (OPN) and Epidermal Growth Factor (EGF) genes on chromosome 6, including a coding sequence of 1509 bp, component of ten exons as code for 502 amino acids (Singh et al., 2020). A transition of Adenine to Guanine at the nucleotide site 746 resulted in the substituting of Glutamine amino acid to Arginine amino acid at location 249 (Q249R) for mutant types (Mulsant et al., 2001; Potki et al., 2020). This mutation in the FecB allele is associated with the additive effect on ovulation rate and litter size in Booroola Merino sheep (Souza et al., 2001; Davis et al., 2002; Guan et al., 2007; Fogarty, 2009). By considering the importance of this gene, many researchers started to screen other prolific sheep breeds to identify it. The BMPR1B mutation has been found, for example, in Garole and Javanese (Davis et al., 2002; Davis, 2005), Hu and Small Tail Han (Hua and Yang, 2009), Kendrapada (Kumar et al., 2008), and Kalehkoohi (Mahdavi et al., 2014) sheep breeds. In many studies, there was a dependency between the FecB gene polymorphism and the litter size (Yang et al., 2010; Chu et al., 2011; Debnath and Singh, 2014; Wang et al., 2018), but in some studies, this association was not significant (Hua et al., 2008; Tian et al., 2009; Hernandez et al., 2019). A meta-analysis including random effects may clear up the heterogeneity between the studies (Dawson et al., 2016, Delphino et al., 2021a, Hossein-Zadeh, 2021, Ambike et al., 2022). A meta-analysis is a statistical technique that combines the results of multiple scientific studies. In other words, meta-analysis is a helpful methodology for incorporating the results obtained in various researches and giving enormous informational data to survey by pooling the consequences of these investigations. In the same manner, by leading meta-analysis, there can be remuneration for a small sample size of single research by expanding the statistical sensitivity and accuracy of assessments (Sutton et al., 2000; Hunter and Schmidt, 2004; Mahmoudi et al., 2019; Delphino et al., 2021b).

A meta-analysis of the influences of the FecB gene polymorphism on the litter size of sheep (Chong et al., 2019) utilized just the Chinese sheep breed. It considered only the FecB genotypes to evaluate the relationship between the litter size and the FecB polymorphism appropriately. Therefore, the present investigation intended to perform a meta-analysis of the associations between litter size and the FecB polymorphism in sheep breeds by applying four genetic models, including the additive, dominant, co-dominant, and recessive models.

Materials and methods

Searching strategy and screening criteria for literature review

Measures from the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist (https://prisma-statement.org/) were used to pick qualified documents for the meta-analysis (Moher et al., 2009).

To locate all related studies in distinct languages, a s ystematic literature search was used for the electronic databases and publications (PubMed, Science Direct, Springer, Web of Science, Google Scholar, Wiley Online Library, CNKI, MagIran, and SID). The following search terms were combined to identify the appropriate studies: 'BMPR1B', 'BMPR-1B', ' Bone Morphogenetic Protein Receptor 1B', 'ALK6', 'Activin Receptor-like Kinase 6', 'fecundity', 'FecB', 'Booroola', 'Gene polymorphism', 'association', 'sheep', ' reproductive traits', 'litter size' and 'prolificacy'. As well, to classify eligible studies which may not have been found in the searching processes, the reference lists of the documents were appropriately investigated.

Criteria of eligibility and method of selection

In the present meta-analysis study, only those studies were incorporated that matched all of the following criteria: (1) supplied allele frequencies and various genotype frequencies of the corresponding litter sizes, (2) stated sample size for each genotype of FecB, (3) assessed the association between the FecB gene polymorphism and the sheep litter size, (4) for each genotype, the least-squares means of litter size were available and (5) the standard error/standard deviation for the least squares means were also reported. The studies have been ruled out whether they're: (i) in summary form; (ii) duplicate studies; (iii) inadequate information; or (iv) review paper.

Data collection process

For extracting the data file, a standard data extraction form was utilized, counting the first author name, sample size, country of the study, year of publication, breed, frequency of genotype, least-square mean, and standard deviation/standard error of each genotype. When the standard deviation (SD) was not available, it was calculated by using the following formula:

$$\mathrm{SD} = \mathrm{SE}\sqrt{\mathrm{N}}$$

where, N is the reported sample size for genotypes and SE is the reported standard error of the mean for genotypes involved in the study. Based on the Cochran methodology (Higgins et al., 2019), the pooled least-squares means (M_{pooled}) and standard deviations (SD_{pooled}) were determined as below:

$$\mathrm{M_{pooled}} = \frac{\mathrm{N_1M_1 + N_2M_2}}{\mathrm{N_1 + N_2}}$$

$$SD_{pooled} = \sqrt{\frac{(N_1-1)SD_1^2+(N_2-1)SD_2^2+\frac{N_1N_2}{N_1+N_2}(M_1^2+M_2^2+2M_1M_2)}{N_1+N_2-1}}$$

where, N_1 and N_2 are the sample sizes reported for two different genotypes, M_1 and M_2 are the least-squares means, and SD_1 and SD_2 are the standard deviations reported for the first and second genotypes, respectively.

Statistical analysis

Statistical analysis was carried out using the metafor package (Viechtbauer, 2010) available in R version 4.1.1(R Development Core Team, 2022). The standardized mean difference (SMD) approach, also known as Cohen's d, was used to measure the effect sizes (Cohen, 2013; Higgins et al., 2019). The four genetic models including additive ("BB" in comparison with "++"), recessive ("BB" in comparison with "B+" and "++"), dominant ("BB" and "B+" in comparison with "++"), and co-dominant ("BB" and "++" in comparison with "B+") were used (Minelli et al., 2005; Lee, 2015; Mahmoudi et al., 2019 ; Razmkabir et al., 2021). The Cochran's Q (Cochran, 1954) and I-squared statistic (I^2) (Higgins et al., 2003) were used to quantify the heterogeneity among the studies. The fixed-effects model was used when the studies were considered homogeneous, while a random-effects model was utilized for heterogeneous studies (DerSimonian and Laird, 1986; Higgins et al., 2003). A fixed-effect model assumes that the differences observed among the studies are caused by chance alone, while the random-effect model assumes that the different studies may have significant variations (Hatala et al., 2005; Chong et al., 2019; Mahmoudi et al., 2020). The sensitivity analysis was done to detect the stability of the overall results by deleting one study at a time. With the aim of testing the publication bias, first of all, to evaluate the asymmetry of the funnel plot, the improved funnel plots with the contour were inspected (Peters et al., 2008) by applying the Egger's intercept test (Egger et al., 1997); a symmetrical funnel plot suggests no publication bias. In addition, the Egger's test was used to quantitatively asses the degree of symmetry of the Funnel plots (Sterne et al., 2011). The trim-and-fill method was used (Duval and Tweedie, 2000) to adjust the estimates for possible publication bias in additive and recessive models. When signs of publication bias were found, the trim-and-fill technique, developed by Duval and Tweedie (2000), was used to correct the possible bias. The changed outcome can be used as a sensitivity analysis to show the degree to which the findings of this research may have been influenced by publication bias (Joober et al., 2012; Mathur and Van derWeele, 2020).

Results

Study selection

The PRISMA flow chart is shown in Figure 1. Surveys of the database and screening of the reference list resulted in 127 and 24 theoretically related researches, respectively. Among them, 23 papers were discarded as duplicates after the preliminary assessment. In addition, 39 reports were in the form of a summary and thus excluded. Among the remaining 89 reports, 63 reports were discarded in total for the reasons stated: (1) the association between the FecB gene polymorphisms and the litter size trait was not investigated, (2) sufficient data such as genotype frequencies, standard deviation, and appropriate mutation were not provided; and (3) focused on other traits, not litter size. Finally, 26 articles with 9902 sheep were chosen for the meta-analysis. There were inquiries of more than one sheep breed in six papers; thus, each breed was considered an independent study. The attributes of the chosen studies are shown in Table 1.

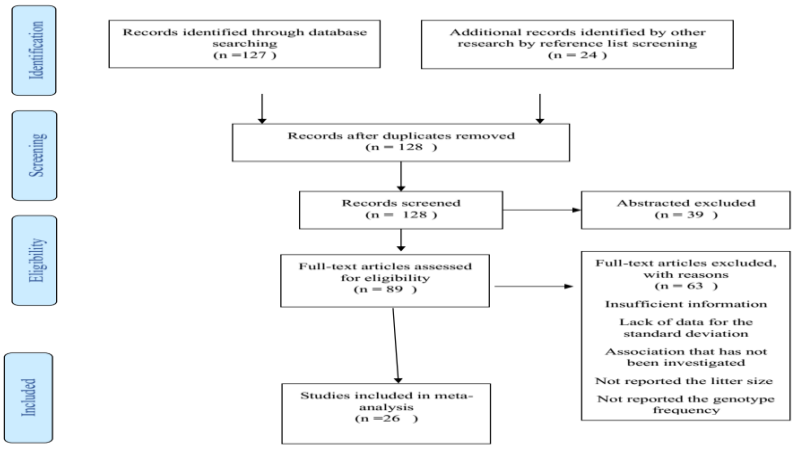

Figure 1. The PRISMA flow chart displaying incorporation and rejection rules

Table1. The genetic influence of the FecB genotypes on litter size was included in this meta-analysis in various sheep breeds.

study ID	Year of publication	Country	Sheep Breed	Genotypes			LSmeans*±SD		
				++	B+	BB	++	B+	BB
(Chen et al. 2015)	2015	China	F2generationsofHanpermutton	13	14	3	1.220±1.370	1.890±2.731	3.000±0.869
(Chu et al., 2011)	2011	China	Han	15	47	78	1.140±0.620	2.160±0.960	2.650±0.971
(Chu et al. 2007)	2007	China	Han	12	78	98	1.250±0.589	2.360±1.060	2.650±0.990
(Hernandez H et al. 2019)	2019	Colombia	OPC	66	75	26	1.270±0.731	1.440±0.866	1.490±0.510
(Debnath and Singh 2014)	2014	India	Shahabadi	24	76	0	1.000±0.441	1.179±0.523	NA*
(Fang et al. 2010)	2010	China	GermanMerino	11	22	14	1.950±0.700	2.060±0.521	2.530±1.160
(Fang et al. 2010)	2010	China	Han	7	35	26	2.220±0.400	2.430±1.420	3.110±0.872
(Fang et al. 2010)	2010	China	GermanMerinocrossHan	10	48	27	1.970±0.440	2.250±1.462	2.830±0.779
(Guan et al. 2007)	2007	China	ChineseMerino	10	16	27	1.230±2.154	2.340±2.508	2.840±3.861
(Jia et al. 2005)	2005	China	PollDorset	76	2	1	1.140±0.349	1.000±0.354	2.000±0.350
(Jia et al. 2005)	2005	China	Han	12	44	45	1.420±0.866	1.930±0.862	2.270±0.872
(Kang et al. 2017)	2017	China	TancrossHan	106	34	11	1.320±0.474	1.410±0.507	1.360±0.501
(Li et al. 2012)	2012	China	Wadi	10	49	37	1.880±1.078	2.380±0.749	2.790±0.669
(Mahdavi et al. 2014)	2014	Iran	Kalehkoohi	30	36	11	1.379±0.745	1.725±0.738	1.902±0.647
(Maskur et al. 2016)	2016	Indonesia	Indonesianfat-tailed	168	67	15	1.145±1.400	1.455±2.079	1.685±0.639
(Pan et al. 2015)	2015	China	Hu	0	12	47	NA	2.020±1.109	2.560±3.976
(Pan et al. 2015)	2015	China	Han	36	117	140	1.750±3.240	2.410±4.651	2.890±11.004
(Ren et al. 2011)	2011	China	Wadi	28	104	54	1.960±1.482	2.490±5.415	2.810±3.079
(Roy et al. 2011)	2011	India	Bonpala	2	22	73	1.500±0.707	1.640±0.582	1.710±0.632
(Shao et al. 2012)	2012	China	ZellerBlack	46	44	10	1.980±0.610	2.660±1.187	3.000±0.819
(Shi et al. 2012)	2012	China	ZellerBlack	160	157	37	1.610±0.898	2.160±0.840	2.210±0.827
(Shi et al. 2012)	2011	China	Duolang	479	82	3	1.570±1.204	2.080±0.833	2.000±0.639
(Sun et al. 2011)	2011	China	Hybridized	16	38	17	1.130±1.400	1.530±3.822	2.250±2.062
(Tian et al. 2009)	2009	China	Tan	165	60	25	1.270±0.951	1.350±0.643	1.430±0.560
(Tian et al. 2009)	2009	China	Han	8	24	36	1.630±0.074	2.290±0.470	2.830±0.378
(Wang and Maimaitiyiming 2011)	2011	China	Duolang	277	95	2	1.520±1.398	2.030±0.926	2.990±0.651
(Wang et al., 2015)	2015	China	Hu	19	685	57	1.150±0.654	1.740±0.680	1.890±0.695
(Wang et al., 2015)	2015	China	Han	19	765	85	1.210±0.741	1.780±0.719	2.060±0.719
(Wang et al., 2018)	2018	China	Hu	12	182	1827	1.746±0.856	2.165±1.889	2.459±5.514
(Yang et al. 2010)	2010	China	Merino	230	177	35	1.270±0.910	1.830±0.798	1.870±0.887
(Yang et al. 2012)	2012	China	Han	128	719	437	1.740±1.697	2.160±4.558	2.720±2.299
(Zhu et al. 2006)	2006	China	Merino	10	28	2	1.600±0.569	2.110±0.571	3.000±0.570
(Zhu et al. 2006)	2006	China	Han	4	17	16	2.250±0.580	2.760±0.569	2.810±0.568

*Lsmeans: The least-squares mean of litter size, SD: standard deviation, NA: Not available.

Heterogeneity assessment between studies

The results of heterogeneity testing by applying the Cochran's Q test and I-squared statistic (I^2) measures across the investigated genetic models are shown in Table 2. Considering the Cochran's Q test, P-values were less than 0.005 under all investigated models (additive, dominant, co-dominant and recessive). The estimated values of I^2 were also greater than 45 % for all the considered models. Therefore, the random-effect model was supposed to study the association between the FecB polymorphism and the litter size of sheep in the present study.

Table 2. Heterogeneity testing of the investigations used in the present study

Genetic model	Q [a]		I^2 [a]		
	Estimated	P-value	Estimated	Lower limit	Upper limit
Additive ('BB' *vs.* '++')	115.23	<0.0001	69.6%	57.3%	78.4%
Dominant ('BB' and 'B+' *vs.* '++')	49.71	0.002	49.7%	20.9%	68 .0%
Co-dominant ('BB' and '++' *vs.* 'B+')	103.20	<0.0001	71.9%	59.5%	80.5%
Recessive ('BB' *vs.* 'B+' and '++')	60.28	0.005	46.0%	21.3%	63.0%

[a] Q: Cochran's Q test, I^2: I-squared statistic

Analysis of sensitivity and assessment of publication bias

Evidence of data distribution asymmetry was shown by visual inspection of funnel plots under the additive and recessive models (Figure 2). It was verified by a substantial Egger intercept test (Table 3). Also, in contrast, under the dominant and co-dominant genetic models, the intercept of Egger's test (Table 3) and funnel plots (Figure 2) showed no significant and no evidence of publication bias, respectively. Under the additive model, nine missing studies were assigned through the trim-and-fill technique, and the mean effect size was corrected from SMD=0.767 to SMD=0.511. Furthermore, nine missing studies for the recessive model were imputed and modified the mean effect sizes from SMD=0.373 to SMD=0.255.

Meta-analysis of the association between the FecB polymorphism and the litter size in sheep

The results of the meta-analysis for the association between the FecB gene and litter size under the investigated models are shown in Table 4. The forest plots for the association between FecB polymorphism and litter size applying the additive, dominant, recessive, and co-dominant models, are shown in Figures 3, 4, 5, and 6, respectively. Under additive (SMD = 0.511, P< 0.0001), dominant (SMD = 0.469, P < 0.0001) and recessive (SMD = 0.255, P < 0.0001) models, the significant effect of FecB genotypes was identified but under the co-dominant (SMD = -0.062, P = 0.3173) model, the association between FecB genotypes and litter size was not significant.

Table 3. The outcomes of Egger's test to survey the prevalence of publication bias

Genetic model	Intercept	P-value
Recessive ('BB' *vs.* 'B+'+'++')	1.21	0.001
Dominant ('BB'+'B+' *vs.* '++')	0.44	0.496
Co-dominant ('BB'+'++' *vs.* 'B+')	0.16	0.840
Additive ('BB' *vs.* '++')	1.42	0.010

Table 4. Meta-analysis of the association of FecB polymorphism with the litter size

Genetic model	No. of breeds	SMD [a]	95% Confidence Interval		P-value
			Lower limit	Upper limit	
Additive ('BB' *vs.* '++')	27	0.511	0.2851	0.7373	< 0.0001
Dominant ('BB' and 'B+' *vs.* '++')	26	0.469	0.3483	0.5908	< 0.0001
Co-dominant ('BB' and '++' *vs.* 'B+')	30	-0.062	-0.1119	0.0529	0.3173
Recessive ('BB' *vs.* 'B+' and '++')	27	0.255	0.1394	0.3716	< 0.0001

[a]SMD: Standardized mean difference

Discussion

The influence of single nucleotide polymorphisms in FecB gene on the litter size in sheep is of great importance. In the FecB coding sequence, a missense substitution (Q249R) is associated with the Booroola phenotype of comparatively greater prolificacy. Although the association between polymorphism in the FecB and the litter size of sheep have been identified in most studies there are still some reports in which the corresponding association was non-significant. These contradictory findings suggest that if a meta-analysis was done, there might be a clearer sense of an SNP-litter size association which might be a helpful tool for evaluating whether FecB gene polymorphism was associated with the litter size of sheep or not.

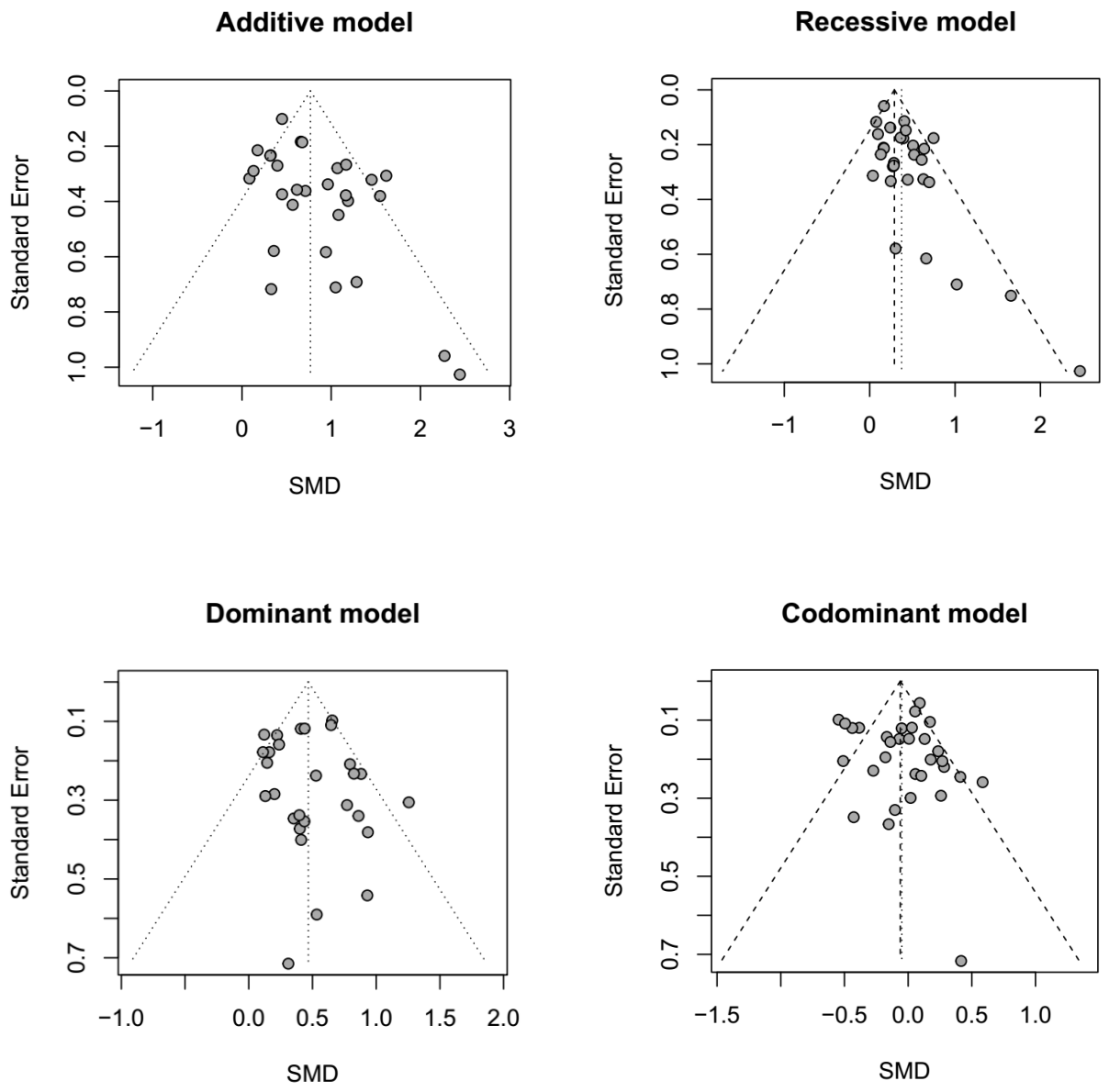

Figure 2. Funnel plot showing the relationship between the observed effect size (standardized mean differences (SMD); solid circles) and its standard error for the investigated different genetic models

A total of 9902 cases of various sheep breeds have been used to assess the influence of the FecB gene on the litter size of sheep. There had been a disparity in the litter size among animals with the 'BB', 'BB' and/or 'B+' genotypes as well as those with genotypes of '++', 'B+' and/or '++' in litter size ($p<0.01$). In addition, by applying the co-dominant model, there was no distinction between the B+ genotype and 'BB and/or ++' genotypes ($P>0.05$). The findings suggested that an increase of approximately 0.47 lambs in litter size (under the dominant model) was associated with the first copy of the FecB gene and an increase of roughly 0.25 lambs with the second copy (under the recessive model) (Figures 4-5). These observations confirmed the findings of several published papers showing the substantial impact of FecB on the litter size in several sheep breeds (Chu et al., 2011; Debnath and Singh, 2014; Mahdavi et al., 2014; Chen et al., 2015). However, the higher effect of one copy of the FecB gene was observed, in comparison with another copy, in the Merino (Zhu et al., 2006), and Duolang (Wang and Maimaitiyiming, 2011) sheep breeds. The sample size of BB genotypes for these breeds was small in magnitude, which may explain, to some extent, their obtained results. Chong et al. (2019) studied the influence of FecB polymorphism on the Chinese sheep litter size by meta-analysis. They indica-

ted that the first and second copies of the gene caused increases of 0.4 to 0.5 lambs in litter size, respectively. The results of the current meta-analysis study were inconsistent with Fogarty (2009), who concluded that the FecB gene increases the litter size, which pointed out that the litter size increased by 0.7 lambs with the first copy of FecB.

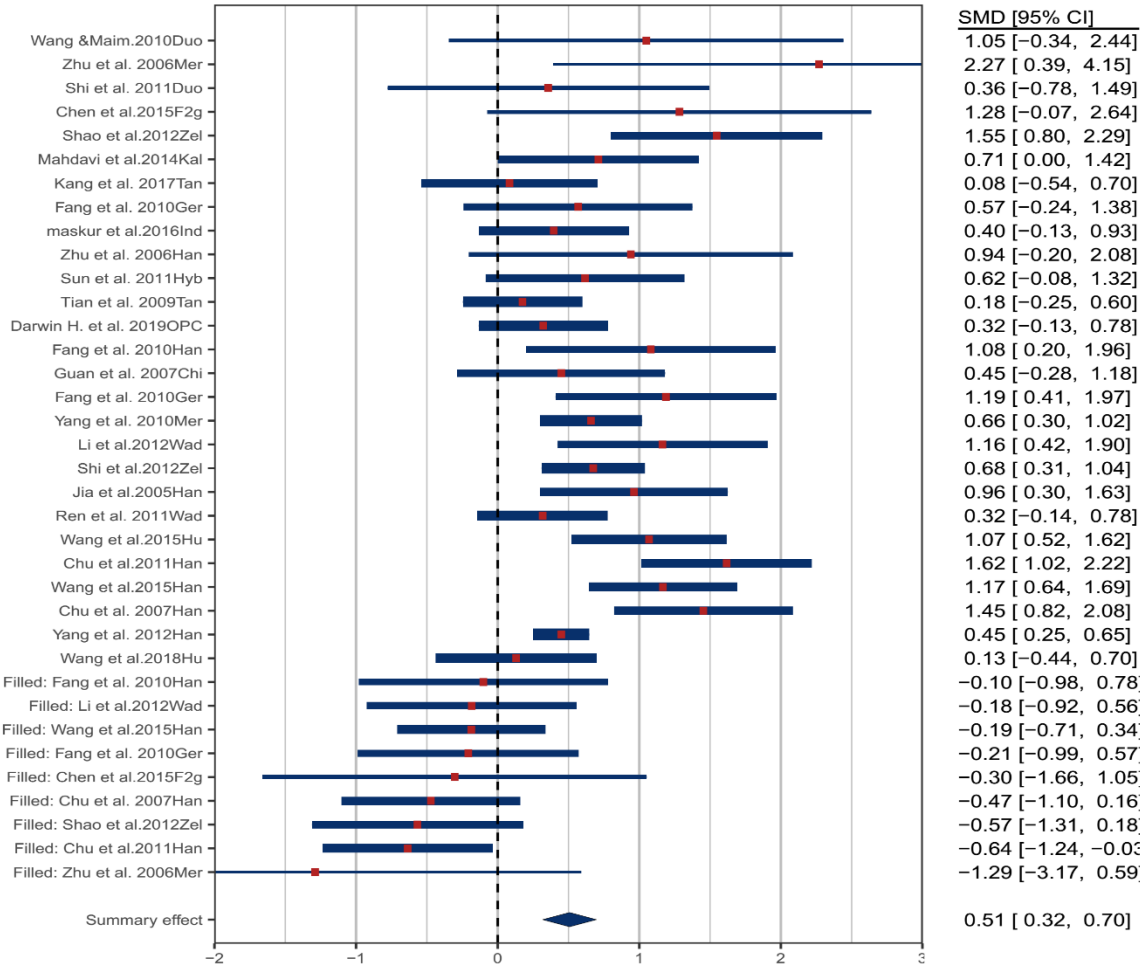

Figure 3. Forest plot for the association between FecB polymorphism and litter size applying the additive model. The thickness and length of the blue rectangles indicate the weight and confidence interval of each study, respectively. The diamond placed at the bottom of the plot illustrates the summary effect.

The present meta-analysis varies in a variety of aspects from the previous meta-analysis conducted by Chong et al. (2019): (i) while in Chong et al. (2019), only Chinese sheep breeds were included, in our study, data from different sheep breeds from different countries were used; (ii) in our study, four distinct genetic models including the additive, dominant, co-dominant and recessive models were used. (iii) 26 qualified studies were included in the current study to evaluate litter size data, while the number of studies used by Chong et al. (2019) was 21; (iv) for this meta-analysis, 9902 records have been used, which is higher than 5089 records used by Chong et al. (2019). Therefore, our meta-analysis was expected to have much greater predictive strength and provides more accurate results.

The current meta-analysis study, however, may have some restrictions: (i) moderate to high research heterogeneity was observed under the utilized genetic models; (ii) the sample sizes of several studies involved were not sufficiently large; (iii) only the influence of genetic factors on sheep litter size has been investigated, though litter size is a complex trait. Accordingly, other factors, including correlative functional genes, SNP-SNP, gene-gene interactions, and environmental effects which affect the litter size in sheep, have to be assessed in future meta-analysis studies.

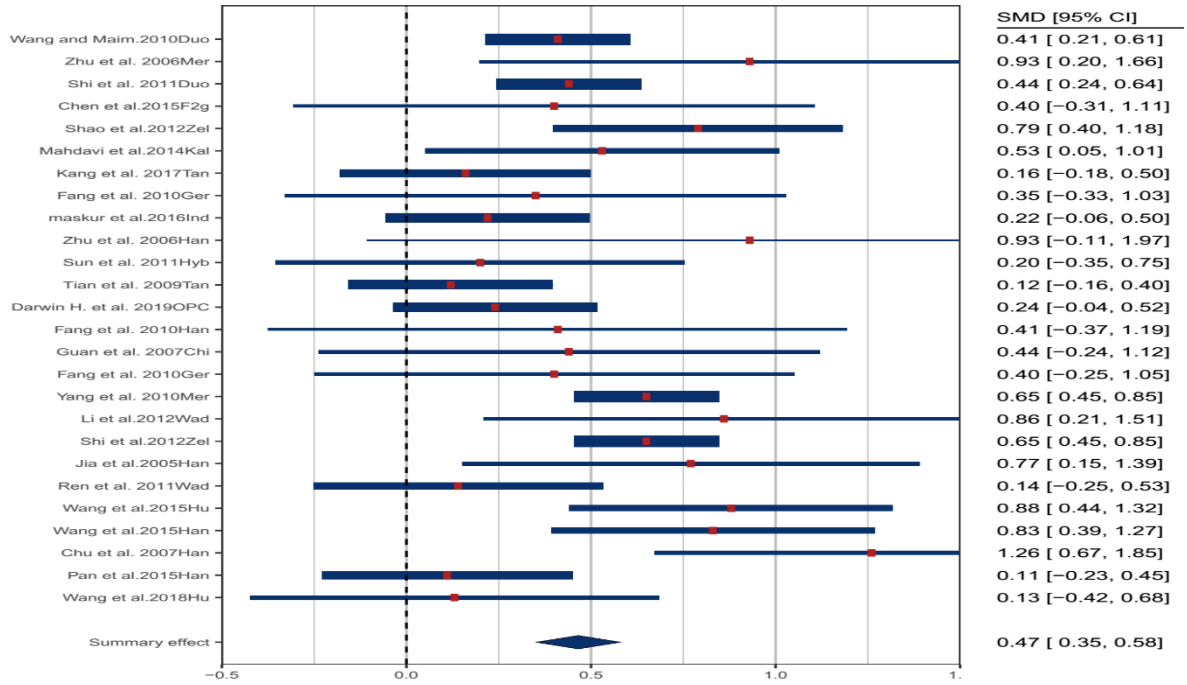

Figure 4. Forest plot for the association between FecB polymorphism and litter size applying the dominant model. The thickness and length of the blue rectangles indicate the weight and confidence interval of each study, respectively. The diamond placed at the bottom of the plot illustrates the summary effect.

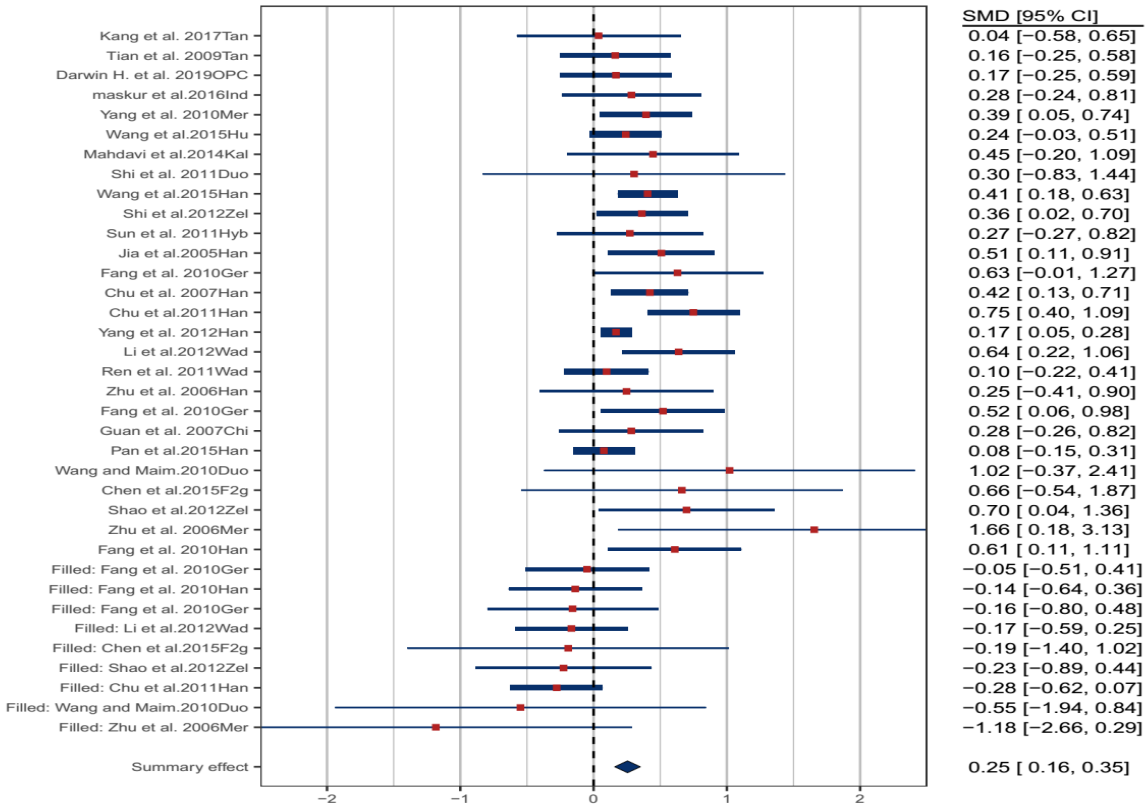

Figure 5. Forest plot for the association between FecB polymorphism and litter size applying the recessive model. The thickness and length of the blue rectangles indicate the weight and confidence interval of each study, respectively. The diamond placed at the bottom of the plot illustrates the summary effect.

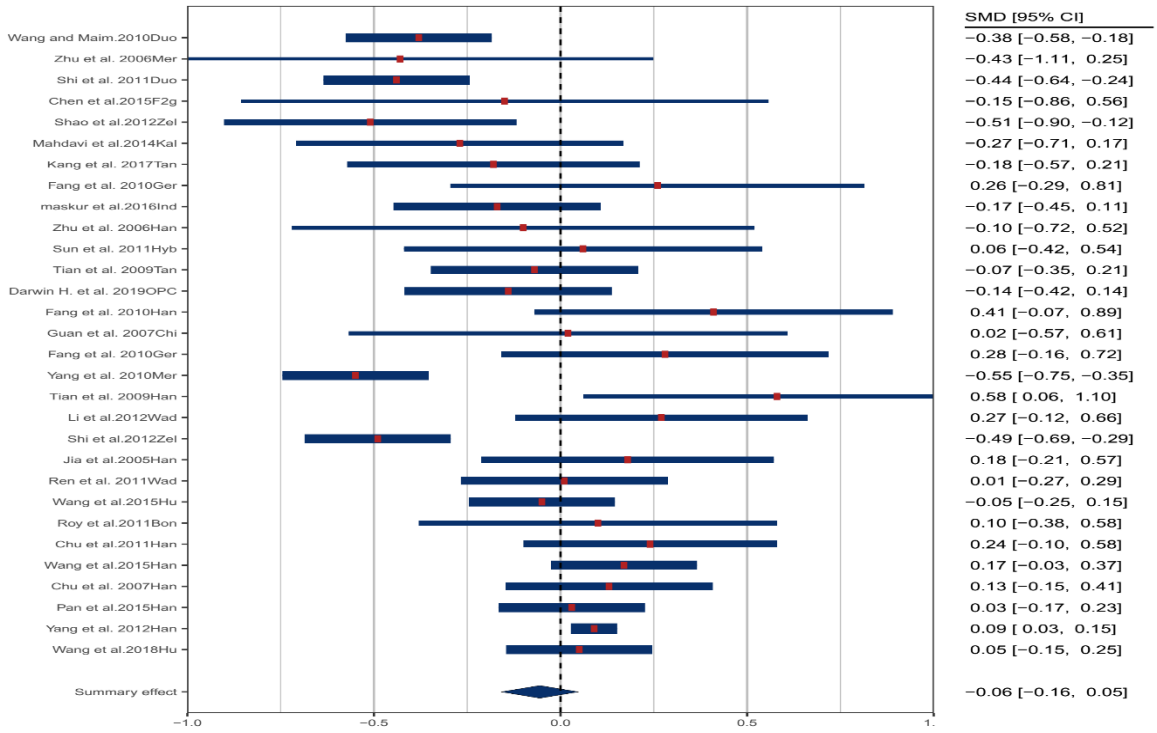

Figure 6. Forest plot for the association between FecB polymorphism and litter size applying the co-dominant. The thickness and length of the blue rectangles indicate the weight and confidence interval of each study, respectively. The diamond placed at the bottom of the plot illustrates the summary effect.

Conclusions

The results of the current study supported the idea that BMPR-IB fundamentally influenced the litter size in sheep. Therefore, it can be utilized in a marker-assisted selection programs to improve the litter size in low reproductive performance sheep breeds. Another efficient strategy can be introgression of this gene in low prolific sheep breeds by crossbreeding.

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