A Meta-analysis Study of Association Between FecB Polymorphism and Litter Size in Sheep

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Abstract

Litter size is perhaps the main commercial trait since it has an observable effect on benefit in the sheep industry. Fecundity genes, play a vital role in expression of litter size. One of the most popular of these genes is the Booroola gene (FecB). In many past researches there was a dependency between the BMPR1B gene polymorphism and litter size of sheep. In the current study, a meta-analysis directed by coalescing outcome of 9902 cases of 26 published research wherein various breeds of sheep to assess the influence of the FecB gene on litter size utilizing additive, recessive, dominant, and co-dominant genetic models. The random effects model was used for data analysis according to the Cochran Q test and I^2 quantity. Under additive (SMD = 0.528), dominant (SMD = 0.468) and recessive (SMD = 0.250) models, the significant effect ($P < 0.01$) of FecB genotypes has been identified. Furthermore, under the co-dominant (SMD = -0.050, $P = 0.3332$) model, the association between FecB genotypes and litter size trait had not been detected. A growth in litter size by about 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 this gene. Consequences of the current study support the idea that BMPR1B fundamentally influenced litter size and subsequently it may be utilized for Marker-assisted selection programmes for improved genetic merit of reproductive futures and furthermore insert this gene by crossbreeding in low prolific breeds may improve reproductive characteristics.

Introduction

Sheep farming is incompetent and unprofitable due to low efficiency. One of the best ways to improve this situation is the improvement of the fecundity and fertility of sheep via selective practices (Li et al., 2021). One of the fundamental reproductive traits in sheep is litter size that is affected by many unknown factors. Because of low heritability of this trait, traditional breeding strategies have been useless to increase it rapidly (Mahdavi et al., 2014; Wang et al., 2015). Consequently, researchers hold sought to seek a number of variants of candidate genes act on litter size that should stand helpful for marker-assisted selection (MAS) and molecular genetics techniques. Findings demonstrated that a range of different genes, commonly termed fecundity (Fec) genes, play an important role on litter size. One of the most popular of these genes is Bone morphogenetic protein receptor type IB (BMPR1B) which is famous as activin-like Kinase 6 or FecB or Booroola gene (Wilson et al. 2001, Chu et al. 2011, Plakkot et al. 2020).

Booroola gene is the 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, result in the substitution 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 Fec B 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, S.-R. Liu, et al., 2007; Fogarty, 2009). Considering the importance of this gene, many researchers started out 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 Kالهكووحي (Mahdavi et al., 2014). However nearly all researches there was a dependency between the FecB gene polymorphism and 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 H 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). Meta-analysis is a helpful methodology for incorporating of results revealed in various researches and to give enormous informational data to survey by pooling the consequences of these investigations. In like manner, by leading meta-analysis, there can be remuneration for a small sample size of single researches through expanding the statistical sensitivity and accuracy of assessments (Sutton et al., 2000; Hunter and Schmidt, 2004; Mahmoudi et al., 2019; Delphino et al., 2021a).

A meta-analysis of the influences of the FecB gene polymorphism on sheep litter size (Chong et al., 2019) utilized just Chinese sheep breeds, and contrasted only FecB genotypes to evaluate appropriately the relationship between litter size and FecB polymorphism. Therefore, the current study intended to do a meta-analysis of relationships of litter size and FecB polymorphism in sheep with four distinct genetic models including the additive, dominant, co-dominant and recessive.

Materials And Methods

Searching strategy and screening criteria for literature review

Criteria from the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist were used to pick qualified documents for the meta-analysis (Moher et al., 2009).

In order to locate all related research studies in distinct languages, a systematic literature search was performed for 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 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 that may not have been found in the searching processes, reference lists of the documents were thoroughly investigated.

Criteria of eligibility and method of selection

In the present meta-analysis study, a research has been incorporated if it only 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) assessing the association between FecB gene polymorphism and sheep litter size, (4) For each genotype, litter size least square means identified and (5) standard error/standard deviation for least square means recorded has been given. 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

To extract data file, a standard data extraction form was utilized, counting the first author name, sample size, country study, year of publication breed, frequency of genotype, least square mean and standard deviation/standard error of each genotype. When the standard deviation was not published it was determined using the following function:

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

where, N is a sample size and SE is the standard error of mean for genotypes. Based on the Cochrane Methodology (Higgins et al., 2019), pooled the least square means and standard deviations were determined as shown below:

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

In which, N1 and N2 are the sample sizes, the least square mean is M1 and M2, and the standard deviations recorded for the first and second classes are SD1 and SD2, respectively.

Statistical analysis

The statistical analysis has been carried out using R (v 4.1.1). To evaluate the effect size, the standardized mean difference (SMD) approach (Higgins et al., 2019) has been used by utilizing additive ("BB" in comparison with "++"), recessive ("BB" in comparison with "B++"), dominant ("BB" in comparison with "++"), and co-dominant ("BB" in comparison with "B+") genetic models, to study the association between litter size and FecB polymorphism in sheep.

The Cochran's Q (Cochran, 1954); and I-squared statistics (I^2) (Higgins et al., 2003, 2019) were used to measure the heterogeneity among included research to ensure that all involved researches are drawn from the identical population. The fixed-effects model was used when the studies are considered homogeneous, while a random-effects model was utilized for heterogeneous studies (DerSimonian and Laird, 1986; Higgins et al., 2003). A fixed effects model assumes that the differences observed among research are caused by chance alone, while the model of random effects assumes that different studies can have significant diversity and tests variations within and between studies (Hatala et al., 2005; Chong et al., 2019). The sensitivity analysis was done to detect the stability of the overall results by deleting one research at a time. To test 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) and Egger's intercept test (Egger et al., 1997) were employed. Where a symmetrical funnel plot suggests no publication bias. In addition, Egger's test was used to quantitatively assessment of the degree of symmetry of the Funnel plots (Sterne et al., 2011). When finding signs of publication bias, use the trim and fill technique of Duval and Tweedie to correct for possible bias (Duval and Tweedie, 2000). In the funnel plot, the trim-and-fill approach tests asymmetry and imputes the number of suspected missing studies. 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 VanderWeele, 2020).

Results

Study selection

In order to provide an overview of the literature survey and research selection at different stages of the assessment process, a PRISMA flow chart was followed (Fig. 1). Surveys of the database and screening of the reference list resulted in 127 and 24 theoretically related research, respectively. Among them, 23 papers were discarded as duplicates after the first assessment. In addition, 39 papers were in the form of a summary; and thus excluded. Of the remaining 89 papers, 63 papers were denied in total for the reasons stated: (1) The association between 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) Concentrated on other traits, not litter size. Finally, 26 articles with 9902 sheep were chosen to be used in the meta-analysis. There were inquiries of more than one sheep breed in six papers thus each breed was considered as a separate research. Table 1 contains the attributes of the chosen research.

Heterogeneity assessment between studies

Table 2 summarizes the results of the application of Cochran's Q heterogeneity test and I-squared statistics (I^2) through every genetic model. Results using the Cochran Q test showed that in all model (Additive, Dominant, Codominant and recessive) P values were less than 0.005. The estimated I^2 was also greater than 45% for all the considered models, Therefore the random effects model was applied to study the relationship of FecB polymorphism and sheep litter size (Higgins et al., 2019).

Analysis of sensitivity and assessment of publication bias

Evidence of data distribution asymmetry was shown by visual inspection of funnel plots in additive and recessive models (Fig. 2). This was verified by a substantial Egger intercept test (Table 4). Also, in contrast, in the dominant and codominant genetic models, intercept of Egger's test (Table 4) and funnel plots (Fig. 2) showed no significant and no evidence of publication bias, respectively. The trim-and-fill method was used (Duval and Tweedie, 2000) to adjust the estimates for possible publication bias in additive and recessive models. For 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=0.528. Furthermore, 10 missing studies for recessive model were imputed and modified mean effect size from SMD=0.373 to SMD=0.250.

Meta-analysis of the relationship of the FecB polymorphism and litter size of sheep

Table 3 and Figs. 3 to 6 illustrate the findings for the association between the FecB gene and the interest trait using the four genetic models. Under additive (SMD = 0.528, $P < 0.0001$), dominant (SMD = 0.468, $P < 0.0001$) and recessive (SMD = 0.250, $P = 0.0011$) models, the significant effect of FecB genotypes has been identified. Furthermore, under the co-dominant (SMD = -0.050, $P = 0.3332$) model, the association among FecB genotypes and litter size trait had not been detected.

Discussion

The influence of single nucleotide polymorphisms in the FecB gene on sheep litter size has been an important field of study, since it is an excellent gene. In the FecB coding sequence, a missense substitution (Q249R) is associated with the Booroola phenotype of comparatively greater prolificacy. While there has been an association between polymorphism in FecB and sheep litter size in most studies, there are still some research where this association has not been identified. 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 correlated with sheep litter size.

A total of 9902 cases wherein various breeds of sheep have been used to assess the influence of the FecB gene on sheep litter size. The findings of the genetic models of additive, dominant and recessive have been shown to have a positive relationship between the interest of FecB gene and litter size (Figs. 3-5). Furthermore, by using the co-dominant model, there has been no association of FecB polymorphism with sheep litter size (Fig. 6).

There had been a disparity 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, with using the co-dominant model for study, there was no distinction between the B+ genotype and 'BB and/or ++' genotypes ($p > 0.05$). The findings suggested that a growth in litter size by about 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 this gene, that in several sheep breeds have been consistently excellent (Fig. 4-5). These observations are in accordance with the finding of several published pieces of research which have shown that it has a substantial impact on the litter size (Chu et al. 2011, Debnath and Singh 2014, Mahdavi et al. 2014, Chen et al. 2015). In general, the influence of the second copy of the fec gene on the Poll Dorset sheep (Jia et al., 2005), Merino sheep (Zhu et al., 2006) and Duolang sheep gene has been further increased (Wang and Maimaitiyming, 2011). The sample size of BB genotypes for these three breeds was so small, which may be the explanation for this occurrence. Chong et al. (2019) studied the influence of FecB polymorphism on Chinese sheep litter size by meta- analysis. They indicated that each gene copy causes a growth in litter size of 0.4 to 0.5 lambs. The findings of this research were consistent with the results of their study. The results of the current meta-analysis were consistent with Fogarty (2009) conclusions that the FecB gene increases the litter size, but he stated that with the first copy of this gene the litter size increased by 0.7. The finding of the study can be clarified in particular, assuming that the FecB gene is not the only factor that controls the litter size, it includes many other factors, such as correlative functional genes, maternal inputs and environmental effects (Davis et al., 2006; Chen et al., 2015). Also, the findings of the current meta-analysis study suggest that certain other sheep breeding molecular markers, including the BMP15, GDF9 genes and others, will also have to be assessed.

Current meta-analysis varies in a variety of respects from the previous meta-analysis conducted by Chong et al. (2019): (i) In their research, they included only Chinese sheep breeds, but this is not the case in the present study; (ii) To perform the studies, four distinct genetic models were used, including the additive, dominant, co-dominant and recessive models, but Chong et al. contrasted only FecB genotypes to evaluate appropriately the associations between FecB polymorphism and litter size; (iii) 26 qualifying studies were included in this current study to evaluate litter size data, while the number of studies used by Chong et al. was 21; (iv) For this meta-analysis, 9902 sheep records have been used, which is higher than the numbers used with 5089 by Chong et al. Such data may be conclusive proof that the latest meta-analysis has much greater predictive strength and provides more accurate results.

In addition, the current meta-analysis has several strengths: (i) all studies published in different language in the meta-analysis literature have been used; (ii) sensitivity analysis has been carried out by eliminating one study at a time to assess the consistency of the outcomes obtained; (iii) To accurately investigate the relationship among the FecB polymorphism and sheep litter size, four distinct genetic models containing additive, dominant, co-dominant and recessive models were used; and (iv) In order to perform the meta-analysis, have pooled a big dataset with 9902 records, which may result in more reliable results than small sample sizes.

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. Precautions should be taken for these considerations when interpreting the findings of this meta-analysis.

In conclusion, consequences of the current review support the idea that BMPR-IB fundamentally influenced litter size and was related to litter size in sheep and subsequently it may be utilized adequately for marker-assisted selection programmers for improving genetic merit of reproductive traits and furthermore introgression of this gene by crossbreeding in low prolific breeds can improve reproductive performance in sheep breeds.

Declarations

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Competing Interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

All authors contributed to the study conception and design. All authors contributed to Material preparation and data collection. Data Analysis was performed by A. Barazandeh. The first draft of the manuscript was written by A. Barazandeh and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data Availability

Not Applicable

Ethics approval

This is an observational study. The XYZ Research Ethics Committee has confirmed that no ethical approval is required.

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Tables

Table 1: The genetic influence of the fecb genotypes on litter size has been 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, S. R. Liu, 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	PolIDorset	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., n.d.)	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

2015)									
(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.									

Table 2: Test findings for heterogeneity of meta-analysis research

Contrasts	Q	I ²			
	Estimated	P value	Estimated	CI_Low	CI_Up
Additive (BB vs '++')	119.00	<0.0001	68.9%	56.6%	77.7%
Dominant ('BB'+B+' vs '++')	49.77	0.005	45.8%	15.4%	65.2%
Co-dominant ('BB'++++ vs 'B+')	103.64	<0.0001	71.1%	58.4%	79.8%
Recessive (BB vs 'B'+'+')	70.38	0.0011	46.0%	21.3%	63.0%

Table 3: Meta-analysis of the association of fecb polymorphism with litter size

Contrasts	No. breeds	SMD	95% Confidence Interval		P-value
			Lower Limit	Upper Limit	
Additive (BB vs '++')	29	0.528	0.2919	0.7635	< 0.0001
Dominant ('BB'+B+' vs '++')	28	0.468	0.3527	0.5826	< 0.0001
Co-dominant ('BB'++++ vs 'B+')	31	-0.050	-0.1539	0.0538	0.3332
Recessive (BB vs 'B'+'+')	29	0.250	0.1070	0.3933	0.0011

Table 4: outcomes of using Egger's test to survey the prevalence of publication bias in meta-analyses

Contrasts	Intercept	P
Recessive (BB vs 'B'+'+')	1.21	0.001
Dominant ('BB'+B+' vs '++')	0.36	0.534
Co-dominant ('BB'++++ vs 'B+')	0.22	0.760
Additive (BB vs '++')	1.42	0.010

Figures

Figure 1

The PRISMA flow chart displaying incorporation and rejection rules

Figure 2

Funnel plot showing the relationship between the observed effect size (Standardized mean differences; solid circles) and its standard error for different genetic models in a meta-analysis

Figure 3

Forest plot for association between FecB polymorphism and litter size applying the additive model for meta-analyses the thickness and length of the blue rectangles indicate the weight and confidence interval of each study, respectively; Diamond placed at underneath of plot illustrates the summary effect

Figure 4

Forest plot for association between FecB polymorphism and litter size applying the dominant model for meta-analyses the thickness and length of the blue rectangles indicate the weight and confidence interval of each study, respectively; Diamond placed at underneath of plot illustrates the summary effect

Figure 5

Forest plot for association between FecB polymorphism and litter size applying the recessive model for meta-analyses the thickness and length of the blue rectangles indicate the weight and confidence interval of each study, respectively; Diamond placed at underneath of plot illustrates the summary effect

Figure 6

Forest plot for association between FecB polymorphism and litter size applying the codominant model for meta-analyses the thickness and length of the blue rectangles indicate the weight and confidence interval of each study, respectively; Diamond placed at underneath of plot illustrates the summary effect