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Review article

Effect of BMPRIB gene on litter size of sheep in China: A meta-analysis

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ABSTRACT

Genes or genetic markers related to litter size have been studied for many years in gene selection or marker-assisted selection experiments. The bone morphogenetic protein receptor IB (BMPRIB) gene is one of the candidate genes for increasing litter size of sheep. Results of studies with different sheep breeds in China have been inconsistent with some confirming significant associations between the BMPRIB gene polymorphism and litter size and with other results being inconsistent with there not being an association. In the present study, a meta-analysis was conducted evaluating 21 studies in which 5089 samples were utilized to analyze the genetic effects of BMPRIB genes on litter size in different sheep breeds in China. Results for weighted mean differences (WMD) among BMPRIB genotypes indicated there was an association between the BPRIB gene polymorphism and litter size. Effects of the BMPRIB gene on litter size are remarkably consistent in many sheep populations of China, with each gene copy being associated with an increase in litter size of 0.4 to 0.5 lambs. There are, however, some populations in which there is no effect of a second copy of the B allele. An example is the Zeller black sheep. Furthermore, in the Tan sheep and its crosses, there was no effect of the BMPRIB gene on litter size. In conclusion, with this study, there is a summarizing of magnitude of BMPRIB gene effects on litter size for sheep breeds in China, and these results provide reference information for consideration in indigenous sheep breeding programs.

1. Introduction

Small ruminants, especially native breed types, are important to the livelihoods of a considerable part of human population in the tropics from a socio-economic perspective (Khodabakhshzadeh et al., 2016; Vajed Ebrahimi et al., 2016). Integrated attempts in terms of management and genetic improvement to enhance production, therefore, are important (Mohammadabadi and Sattayimokhtari, 2013; Zamani et al., 2015). Economic and biological efficiency of sheep production enterprises generally is greater when productivity and reproductive performance of ewes is greater (Mohammadabadi and Sattayimokhtari, 2013).

Litter size is an important reproduction trait in sheep breeding and production (Gholibeikifard et al., 2014). The genetic mechanisms controlling litter size in domestic sheep, however, are not completely understood. Three fecundity genes have been identified in sheep, namely bone morphogenetic protein receptor type 1B (BMPR1B; or activin receptor-like kinase 6, ALK6) known as FecB on chromosome 6

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(Mulsant et al., 2001; Wilson et al., 2001), growth differentiation factor 9 (GDF9) known as FecG on chromosome 5 (Nicol et al., 2009), and bone morphogenetic protein 15 (BMP15) known as FecX on chromosome X (Galloway et al., 2000; Moghadaszadeh et al., 2015). Bone morphogenetic protein genes (BMPs) are members of the transforming growth factor-beta (TGF-β) super-family which are multifunctional cytokines with a two-fold function and genes for this protein are expressed in a variety of cells. The BMPs were originally found to have functions in production of ectopic bone formation when the protein extracts with key components of BMP were implanted into the soft tissue *in vivo* (Wozney et al., 1988). The BMPs have important functions in embryonic development, homeostasis, repairing of various tissues, cell differentiation, and apoptosis (Moghadaszadeh et al., 2015). Moghadaszadeh et al. (2015) also studied the polymorphism in Exon 2 of the BMP15 gene and its association with litter size in Raini Cashmere goats, There was an effect of the genotype on litter size ($P < 0.01$) and the does with heterozygote genotypes had the largest litter size, indicating this polymorphism could be used as a molecular marker to improve the prolificacy in Raini Cashmere goats. There was a mutation of the GDF9 gene detected in Icelandic Thoka sheep. This mutation is a single base change (A1279C) resulting in a nonconservative amino acid change (S109R) in the C-terminus of the mature GDF9 protein, with the gene for this protein being normally expressed in oocytes at all stages of development. Genotyping all animals for which reproductive records were available confirmed this mutation to be associated with increased fecundity in heterozygous and with infertility in the homozygote ewes (Nicol et al., 2009).

Using molecular genetics methods similar to DNA markers is one of the more desirable options for more rapid genetic improvements in animal breeding programs. Furthermore, a species without abundant genetic diversity is thought to be unable to cope with changing environments or evolving competitors and parasites (Mohammadabadi et al., 2017). In addition, the capacity of a population to respond adaptively to environmental changes depends on its genetic variability or diversity (Soufy et al., 2009). Thus, genetic diversity in indigenous breeds is very important considering the necessity of preserving what may be a phenotypic uniqueness that is consistent with what is desired for developing a new product (fiber or meat). Conservation should be based on a knowledge base of the genetic resources of the specific breed. It, therefore, is important to attempt to genetically characterize indigenous breeds and utilize the applications of molecular genetics for developing phenotypes that produce these unique products (Mousavizadeh et al., 2009).

Because of it being a well-known gene, the effect of the BMPRIB gene on litter size of sheep has been a major area of study for a long time (Mulsant et al., 2001; Wilson et al., 2001). A non-synonymous substitution (Q249R) in the BMPRIB coding sequence was reported to be associated with the a relatively greater prolificacy Booroola phenotype (Mulsant et al., 2001). Although in most studies there was an association between the BMPRIB gene polymorphism and litter size of sheep (Zhu et al., 2006, Chu et al., 2007; Fang et al., 2010), there are also some studies where there was not this association detected. For example, there was no significant association of the BMPRIB gene polymorphism with litter size in some sheep breeds such as the Tan, Dorset, Suffolk and Merino (Chen et al., 2008; Tian et al., 2009).

More importantly, results have been inconsistent in studies on the effect of the BMPRIB gene in Chinese sheep breeds. A meta-analysis study, therefore, is warranted in which there can be a larger data base utilized to more precisely evaluate the effects of the BMPRIB gene polymorphism on litter size of sheep in China. The results were expected to provide more reliable reference information for indigenous sheep breeding programs.

2. Materials and methods

The data of this study were all collected from two online databases (PubMed and Google scholar), so this study did not involve any ethical issues of laboratory or domestic animals.

2.1. Search strategy and selection criteria

The PubMed database and Google scholar were used to conduct literature searches for relevant studies. Furthermore, there was a review of the retrieved articles using these procedures to search for reports of additional relevant studies. A study was included in this meta-analysis only if it met all the following inclusion criteria: (1) evaluation of the association of the BMPRIB gene polymorphism with litter size of sheep; (2) provided allele frequencies, and the respective litter sizes in ewes with different allelic frequencies with standard deviations.

2.2. Data extraction

The data were independently extracted by two researchers (YQ Chong and GQ Liu) and assessed by another researcher. The following information was extracted from all documents: name of the first author, year of publication, country or region research was conducted, sample size, breed, genotype frequency, litter size and standard deviation (Tables 1 and 2).

2.3. Statistical analysis

The heterogeneity among all studies in this meta-analysis, including the differences between pairs of genotypes, average litter size etc., was assessed using four methods: χ^2 test, Cochran's Q test, H statistic and I^2 statistics, and calculated using the following functions 1, 2, 3 and 4, respectively (Bangert-Drowns and Robert, 1986; Egger et al., 1997; Yang and Zheng, 2005). The use of the Cochran's Q test for this purpose is limited in that it may not be effective when studies have included few samples, thus, it may be difficult to reject the null hypothesis even if it is false. Furthermore, the use of the Cochran's Q test may not be effective when sample sizes are very large, thus, small and unimportant differences in magnitude of effect may result in P values that are typically

Table 1
Main characteristics of all studies of BMPRIB genotypes included in the meta-analysis.

Study ID	Country or Region	Number of observations	Breed	Genotype frequency		
				++	B+	BB
Zhu et al. (2006)	China	37	Small Tail Han sheep	0.11	0.46	0.43
		40	Merino sheep	0.25	0.70	0.05
Chu et al. (2007)	China	188	Small Tail Han sheep	0.07	0.41	0.52
Guan et al. (2007)	China	53	Merino sheep	0.51	0.30	0.19
Tian et al. (2009)	China	68	Small Tail Han sheep	0.12	0.35	0.53
		250	Tan Sheep	0.66	0.24	0.10
Yang et al. (2010a, 2010b)	China	30	Small Tail Han sheep	0.10	0.17	0.73
Fang et al. (2010)	China	72	Small Tail Han sheep	0.10	0.49	0.37
		47	German Merino	0.23	0.47	0.30
		85	German Merino × Small Tail Han sheep	0.12	0.57	0.32
Wang and Maimaitiyiming (2010)	China	374	Duolang sheep	0.74	0.25	0.01
Yang et al. (2010a), 2010b	China	442	Merino sheep	0.52	0.40	0.08
Shi et al. (2011)	China	500	Zeller black sheep	0.45	0.44	0.11
		564	Duolang sheep	0.85	0.15	0.01
Chu et al. (2011)	China	140	Small Tail Han sheep	0.10	0.34	0.56
Sun et al. (2011)	China	71	HybridizedSheep	0.23	0.54	0.24
Ren et al. (2011)	China	186	Wadi sheep	0.15	0.56	0.29
Yang et al. (2012)	China	1284	Small Tail Han sheep	0.10	0.56	0.34
		227	Small Tail Han sheep	0.05	0.48	0.47
Shao et al. (2012)	China	100	Zeller black sheep	0.46	0.44	0.10
Li et al. (2012)	China	98	Wadi sheep	0.10	0.50	0.38
Shi et al. (2012),	China	354	Zeller black sheep	0.452	0.443	0.105
Chen et al. (2015)	China	152	F2 generation of Hanper mutton sheep	0.430	0.430	0.140
Pan et al. (2015)	China	293	Small Tail han sheep	0.123	0.399	0.478
		59	Hu sheep	0.000	0.203	0.797
Wang et al. (2015)	China	869	Small Tail han sheep	0.020	0.880	0.100
		761	Hu sheep	0.020	0.900	0.080
Kang et al. (2017)	China	57	Tan × Han hybrid F1	0.660	0.270	0.070

++, noncarriers $FecB^{+}/FecB^{+}$ of the $FecB^{B}$ Booroola mutation; B+, heterozygous $FecB^{B}/FecB^{+}$ of the $FecB^{B}$ Booroola mutation; BB, homozygous $FecB^{B}/FecB^{B}$ of the $FecB^{B}$ Booroola mutation; Hybridized Sheep, the cross of (F2 generation from Dorper × Small Tail Han sheep)♂and (F1 generation from Dorper × Small Tail Han sheep)♀.

considered from a statistical perspective to be significant (Hatala et al., 2005). With the use of the H and I^2 statistics, the degrees of freedom are considered to correct for the effects of the number of research studies on the Q value. The value of H and I^2 statistics does not change with the number of studies, therefore, the heterogeneity test results are more robust and reliable.

2.3.1. χ^2 test

$$d_i = \frac{\bar{x_{1i}} - \bar{x_{2i}}}{s_{ci}},\ i = 1,2,3...k$$

$$s_{ci} = \sqrt{\frac{(n_{1i}-1){s_{1i}}^2 + (n_{2i}-1){s_{2i}}^2}{n_{1i}+n_{2i}-2}}$$

The d_i and s_{ci} terms are the standardized mean difference and pooled variance, respectively; k is the number of studies in the meta-analysis conducted in the present study; n_{1i} and n_{2i}, $\bar{x_{1i}}$ and $\bar{x_{2i}}$, s_{1i} and s_{2i} are the number, means, standard deviation of samples in the i study, respectively.

$$W_i = n_{1i} + n_{2i}$$

$$\bar{d} = \frac{\sum w_i d_i}{\sum w_i}$$

The w_i and $\bar{d}$ terms are the weighted coefficient and weighted mean, respectively.

$$S_d^2 = \frac{\sum w_i d_i^2 - \bar{d}^2 \sum w_i}{\sum w_i}$$

$$S_e^2 = \frac{4k}{\sum w_i}\left(1 + \frac{\bar{d}^2}{8}\right)$$

Table 2
Genetic effect of BMPRIB genotype on litter size in different sheep breeds included in the meta-analysis.

Study ID	Breed	++			B+			BB		
		SZ	LSM	SD	SZ	LSM	SD	SZ	LSM	SD
Zhu et al. (2006)	Small Tail Han sheep	4	2.25	0.58	17	2.76	0.57	16	2.81	0.57
Zhu et al. (2006)	Merino sheep	10	1.60	0.57	28	2.11	0.57	2	3.00	0.57
Chu et al. (2007)	Small Tail Han sheep	13	1.25	0.62	77	2.36	1.05	98	2.65	0.99
Guan et al. (2007)	Merino sheep	27	1.23	3.54	16	2.34	2.51	10	2.84	2.35
Tian et al. (2009)	Small Tail Han sheep	8	1.63	0.74	24	2.29	0.47	36	2.83	0.38
Tian et al. (2009)	Tan Sheep	165	1.27	0.95	60	1.35	0.64	25	1.43	0.56
Yang et al. (2010a, 2010b)	Small Tail Han sheep	3	2.33	0.58	5	2.91	0.44	22	3.60	1.88
Fang et al. (2010)	Small Tail Han sheep	7	2.22	0.40	35	2.43	1.42	26	3.11	0.87
Fang et al. (2010)	German Merino	11	1.95	0.70	22	2.06	0.52	14	2.53	1.16
Fang et al. (2010)	German Merino × Small Tail Han sheep	10	1.97	0.44	48	2.25	1.46	27	2.83	0.78
Wang and Maimaitiyiming (2010)	Duolang sheep	277	1.52	1.40	95	2.03	0.93	2	2.99	0.65
Yang et al. (2010a), 2010b	Merino sheep	230	1.27	0.91	177	1.83	0.80	35	1.87	0.89
Shi et al. (2011)	Zeller black sheep	225	1.61	1.06	221	2.16	0.99	54	2.21	1.00
Shi et al. (2011)	Duolang sheep	479	1.57	1.20	82	2.08	0.83	3	2.00	0.64
Chu et al. (2011)	Small Tail Han sheep	14	1.14	0.60	48	2.16	0.97	78	2.65	0.97
Sun et al. (2011)	Hybridized Sheep	16	1.13	1.40	38	1.53	3.82	17	2.25	2.06
Ren et al. (2011)	Wadi sheep	28	1.96	1.48	104	2.49	5.41	54	2.81	3.08
Yang et al. (2012)	Small Tail Han sheep	128	1.74	1.70	719	2.16	4.56	437	2.72	2.30
Yang et al. (2012)	Small Tail Han sheep	11	2.07	0.51	109	2.57	2.51	107	3.20	1.76
Shao et al. (2012)	Zeller black sheep	46	1.98	0.61	44	2.66	1.19	10	3.00	0.82
Li et al. (2012)	Wadi sheep	10	1.88	1.08	49	2.38	0.75	37	2.79	0.67
Shao et al. (2012)	Zeller black sheep	46	1.98	0.61	44	2.66	1.19	10	3.00	0.82
Shi et al. (2012)	Zeller black sheep	160	1.61	0.90	157	2.16	0.84	37	2.21	0.83
Chen et al. (2015)	F2 generation of Hanper mutton sheep	13	1.22	1.37	14	1.89	2.73	3	3.00	0.87
Pan et al. (2015)	Small Tail Han sheep	36	1.75	3.24	117	2.41	4.65	140	2.89	11.00
Pan et al. (2015)	Hu sheep	/	/	/	12	2.02	1.11	47	2.56	3.98
Wang et al. (2015)	Small Tail Han sheep	19	1.21	0.17	765	1.78	0.03	85	2.06	0.08
Wang et al. (2015)	Hu sheep	19	1.15	0.15	685	1.74	0.03	57	1.89	0.09
Kang et al. (2017)	Tan × Han hybrid F1	106	1.32	0.47	34	1.41	0.51	11	1.36	0.50

SZ, sample size; LSM, the least squares mean of litter size; SD, standard deviation.

$$\chi^2 = \frac{kS_d^2}{S_e^2}$$

The S_d^2 term is the estimate of weighted variance; and the S_e^2 terms are the calibration factors of heterogeneity.

2.3.2. Cochran's Q test

The formula of the Cochran's Q test is:

$$w_i = \frac{1}{{s_{ci}}^2}$$

$$\bar{T} = \frac{\sum w_i x_i}{\sum w_i}$$

$$Q = \sum W_i (x_i - \bar{x})^2$$

2.3.3. H statistic

The formula of the calculating the H Statistic is:

$$H = \sqrt{\frac{Q}{k-1}}$$

2.3.4. I^2 statistics

The formula of the calculating the I^2 statistics is:

$$I^2 = \frac{H^2 - 1}{H^2}$$

The χ^2 and Q statistics were weighted by the numbers of observations, and those of H and I^2 statistics were weighted by both the numbers of studies and observations involved in meta-analysis. For the χ^2 and Q statistics, the P value > 0.05 was indicative that the

null hypothesis of the heterogeneity test was accepted (no heterogeneity). For the H statistics, $H = 1$ indicates there was no heterogeneity in the meta-analysis; $H > 1.5$ or $H < 1$ indicates there was heterogeneity; and if $1.2 < H < 1.5$, when the 95% CI of H included 1, there was no way to confirm whether heterogeneity existed among the studies, otherwise, there was considered to be heterogeneity among the studies. For the I^2 statistic, an $I^2 < 25\%$ indicates there was a small amount of heterogeneity among studies; 25%–50% was considered to indicate there was moderate heterogeneity among studies; and a value of greater than 75% was considered to indicate there was a large amount of heterogeneity among studies (Higgins et al., 2003; Hatala et al., 2005).

When there was a large amount of heterogeneity, the fixed effect model for meta-analysis should be used (Rosenthal and Rubin, 1982), otherwise the random effect model should be used (Der Simonian and Laird, 1986). With use of the fixed effect model, there is the assumption that the observational effect of all studies, which is only affected by sampling errors, is the same as the true effect (Brockwell and Gordon, 2001; Doi et al., 2015). The fixed-effect model is more rigorous for the background of each study, and only suitable for the "idealized" research background. For example, the fixed-effect model requires that all factors, such as age, weight, and the conditions of health, feeding and environmental, be consistent for all sheep involved in this study. A random effect model, however, allows the true effect to vary across studies, with the mean true effect the parameter of interest. The magnitude of the true effect depends not only on the sampling error of the sample, but also on many aspects of the research design or implementation, such as study object, sample size, data measurement etc. (also known as heterogeneity). The effect of the fixed effect model is determined only by sampling error, while the effect of random effect model is determined by sampling error and the actual error between different studies. The total effect of the random effect model is the average value of each research effect, not only focusing on the research where there was a large sample size, but to balance the effect of each study. When there is obvious heterogeneity among the studies, the random effect model can be used to improve the accuracy of the confidence interval and test efficiency (Wei and Dong, 2006).

3. Results

3.1. Study characteristics

A total of 21 articles with 5089 samples were identified by reviewing potentially relevant articles (Fig. 1). The sample size in these studies varied from 30 to 869, with a mean ± standard deviation (SD) of 195.73 ± 214.63. The characteristics of the selected studies are included in Tables 1 and 2.

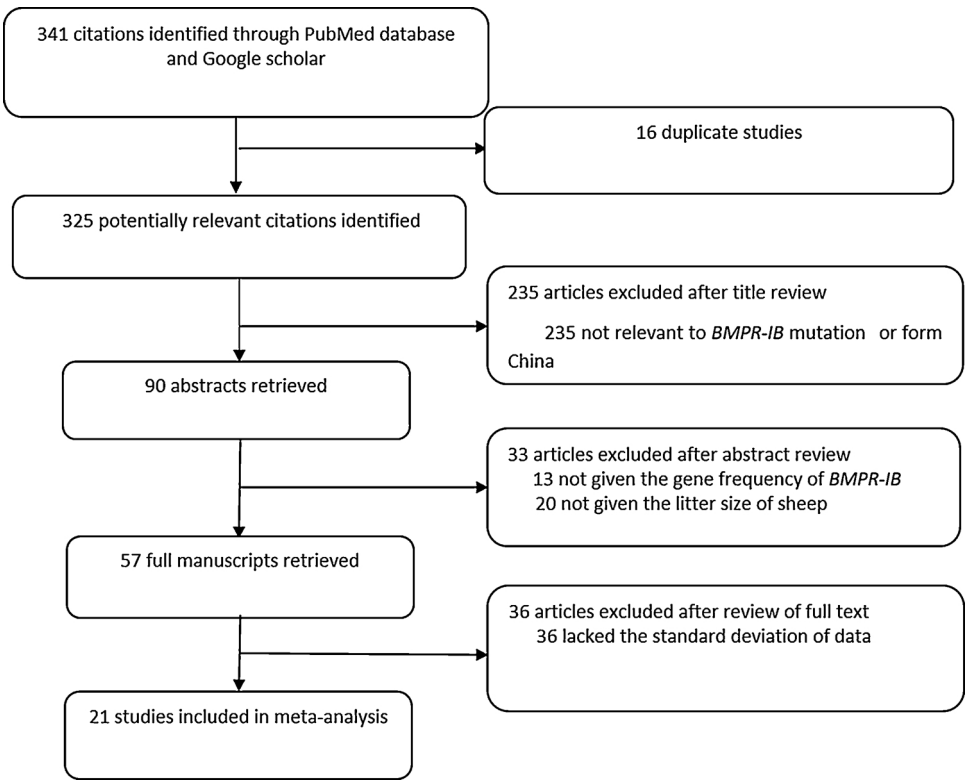


Fig. 1. Flow diagram of the study selection process.

Table 3
Results of test for heterogeneity among studies in the meta-analysis.

Contrasts	χ^2		Q		H		I^2			
	Estimated	P	Estimated	P	Estimated	CI	Estimated	CI		
BB to ++	2131.081	< 0.05	93.75	< 0.0001	1.86	1.54	2.25	71.2%	57.9%	80.3%
B+ to ++	20,390.388	< 0.05	61.03	0.0002	1.50	1.22	1.86	55.8%	32.4%	71.1%
BB to *B*+	7670.201	< 0.05	113.98	< 0.0001	2.02	1.69	2.41	75.4%	64.9%	82.8%

3.2. Heterogeneity analysis of all studies in the meta-analysis

The heterogeneity analysis of this meta-analysis is summarized in Table 3. The χ^2 value of three contrasts with the heterogeneity analysis (BB compared with ++, B + compared with ++, and BB compared with B+) were both larger than χ^2 ($df = 24$, 0.05; $P < 0.05$). The results with use of the Cochran's Q test indicated the *P* values of three contrasts were all less than 0.001. With use of the *H* and I^2 test, the results indicated that there was heterogeneity for all the contrasts with this meta-analysis (*H* and I^2 values were all larger than 1.5% and 25% for the three contrasts, respectively). Those results indicated that the null hypothesis that there was no heterogeneity was rejected and, therefore, a random-effects model was used to proceed with the meta-analysis.

3.3. Publication bias

The funnel plot and Egger's test were used to quantitatively evaluate the publication bias (Fig. 2; Sterne et al., 2011). The results with use of the funnel plots indicated findings in all studies were, for the most part uniformly distributed, except for the contrast BB compared with B + . The results with use of the Egger's test provided statistical evidence for funnel plot symmetry ($P = 0.346$ for *BB* compared with ++, 0.561 for *B*+ compared with ++, and 0.374 for *BB* compared with *B*+, respectively) in overall results, indicating the absence of publication bias. Considering that the funnel plot is a qualitative inspection method, it can be affected by subjective factors. The quantitative results with use of the Egger' test, therefore, were more credible. In brief, there was no significant publication bias detected using the meta-analysis techniques utilized in this study.

3.4. Meta-analysis of BMPRIB gene polymorphism and litter size of sheep

As depicted in Fig. 3, the effects of the BMPRIB gene on litter size were remarkably consistent in many sheep populations of China, with each gene copy resulting in an increase in litter size of 0.4 to 0.5 lambs, apart from some populations in which there was no effect as a result of the second copy this gene. For example, this was the case with the Zeller black sheep. Furthermore, in the Tan sheep and in ewes that were developed by crossbreeding with this breed, there was no effect of the BMPRIB gene on litter size.

4. Discussion

Generally, results for a meta-analysis study are based on the published literature in which there tends to be reporting of the statistically significant conclusions, that is, research with no statistical significance is less likely to be published, which is the publication bias often incurred in meta-analysis studies (Berlin, 1988; Counsell and Fraser, 1995; Dickersin, 1997). The qualitative funnel plot method and quantitative Egger's test method were used to assess for publication bias in the present study. The results of funnel plots indicate that in all studies there was, for the most part, uniformly distributed data indicating there was no publication bias, except for the contrast of BB compared with B + . The results using the Egger's test indicated there was an absence of publication bias in the experiments included in the present meta-analysis. There may be two reasons for the inconsistent results. Firstly, the funnel plot is utilized as a qualitative inspection method, therefore, results can be affected by subjective factors, and the test efficiency of it is less than with use of the Egger's test. Secondly, the asymmetry of funnel diagrams may result not only from publication bias, but also from heterogeneity of the data. The results with use of the Egger's test indicated that there was no significant publication bias affecting results of the present meta-analysis study.

With meta-analysis, although all the studies focus on the same problem or have the same research hypothesis, there are usually differences from each other in many aspects of research design or individual study implementations, such as study objectives, sample size, data determinations etc. This leads to the difference of "scale of effect" among different studies. The statistical heterogeneity is a consequence of clinical heterogeneity (e.g., differences among individuals) and methodological heterogeneity (e.g., differences in study designs, sources of bias) (Seidenfeld et al., 2006) and used to describe the extent of the variation of the effects of a series of studies. A moderate statistical heterogeneity was detected among all studies with use of the meta-analysis in the present study. Before drawing a conclusion from the results, the origin of the heterogeneity should be clarified. There are two hypotheses in this regard that might explain the heterogeneity. The first hypothesis is that the sample size of experiments contributes to the heterogeneity. Data obtained from studies with larger numbers of animals are more precise in values obtained than those with smaller numbers, however, the sample size used in experiments affects the heterogeneity of data among studies, but the specific effect of the sample size is complicated (Topol and Califf, 1992). The second hypothesis is that the results of the meta-analysis are affected by a variety of factors that affect results derived with use of the meta-analysis, including breed, parity, surrounding conditions where study is conducted

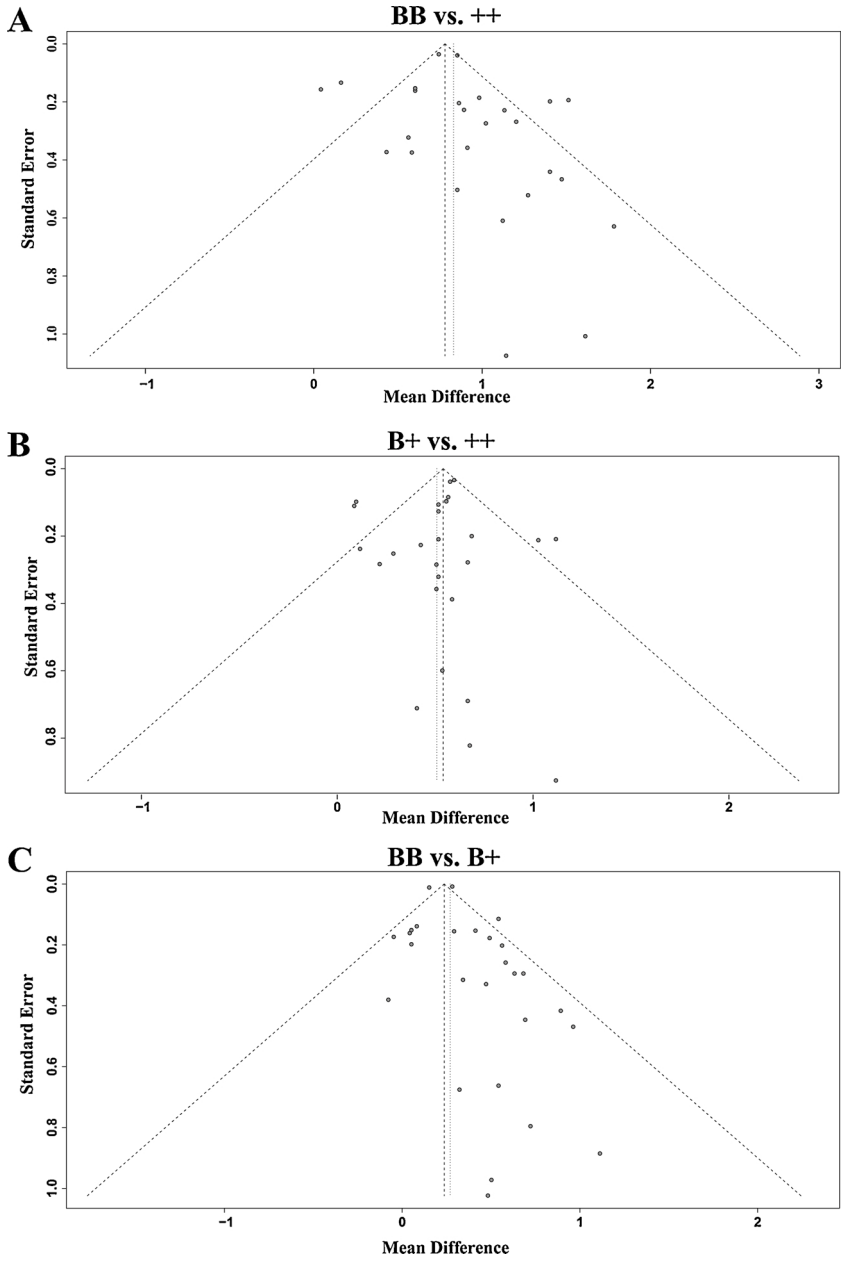
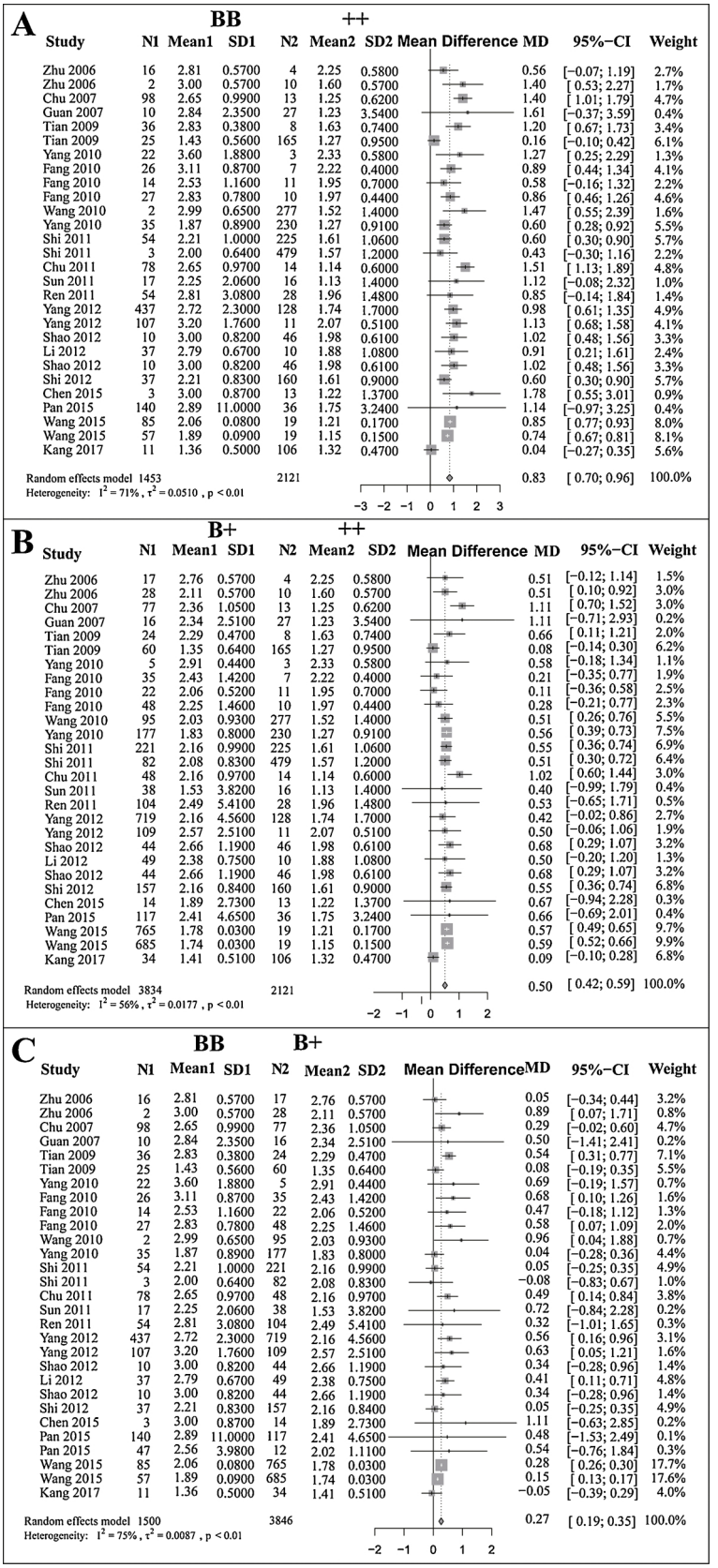


Fig. 2. Funnel plot of BMPRIB polymorphism and litter size of sheep for publication bias.

and climate. For example, the differences in sheep breed (greater compared lesser fertility), parity (primiparity compared with multiparity) and climate (colder compared with hotter ambient temperatures) may affect the litter size and these factors may interact with the effects of the protein encoded by the BMPRIB gene. A systematic review of studies where there was a common question will inevitably result in collection of information with a diversity in results (Higgins and Thompson, 2002). These factors result in a heterogeneity among studies, and may affect the results when these studies are used for a meta-analysis.

A limitation with the use of the meta-analysis in the present study also needs to be acknowledged: the studies included in the meta-analysis were published only in the English and Chinese languages, while the studies published in other languages were ignored. Nevertheless, the results of the present meta-analysis are credible based on the analysis of the heterogeneity and the publication bias which were evaluated through use of the funnel plot and quantitative Egger's test.

A total of 5089 samples in which there was use of 21 sheep breeds in China were used to analyze the BMPRIB gene effects on the litter size. The results indicate there is a significant association between BMPRIB gene polymorphism and litter size of sheep (WMD = 0.82 for BB compared with ++, 0.50 for B + compared with ++, and 0.27 for BB compared with B+, respectively), which were remarkably consistent in many sheep breeds in China. For example, in the Small Tailed Han and Wadi sheep each copy of



(caption on next page)

Fig. 3. Forest plot of the BMPRIB polymorphism and litter size of sheep; Studies are plotted according to the last name of the first author and followed by the publication year in parentheses; Horizontal lines represent 95% CI; Each square represents the WMD point estimate and its size is proportional to the weight of the study Diamond (and broken line) represents the overall summary estimate, with confidence interval given by its width; Weight (%) and overall effect (95% Confidence Interval) and its tests are shown for random effects models.

the BMPRIB gene was associated with an increase in litter size by 0.4 to 0.5 lambs. These results are consistent with results from some previous studies (Chu et al., 2007 and 2011). In particular, there was a further increase of the effect of one copy of the gene with the second copy in Merino sheep (WMD = 0.51 for B + compared with + +, and 0.89 for BB compared with B+, respectively) and Duolang sheep (WMD = 0.51 for B + compared with + +, and 0.96 for BB compared with B+, respectively). The sample size of BB genotype individuals in these two breeds is very small, therefore, there is need for increasing the sample size to further assess the results of the present study. Inconsistent with this finding is that there was a decrease by about half the effect when there was one copy of the BMPRIB gene present when there was a second copy present in some breeds. For example, this was the situation with the Zeller black sheep based on findings in the present study, which is consistent with the results of Fogarty (2009) where litter size increased by 0.5 to 1.3 with the first copy of this gene (B + compared with + +)and with the second copy (BB compared with B+) except for when there is a second copy in the Chinese and Indian sheep breeds. The difference in the results from the present meta-analysis study and the results from these previous studies is that it was concluded that the genetic effect of the second copy was much greater than that of the first copy in Chinese and Indian sheep breeds. This, however, is inconsistent with the results from the present study with results from this study indicating the Zeller black sheep may originate from a different ancient sheep compared with some other Chinese sheep breeds. In particular, in the Tan sheep and in ewes resulting from crossbreeding using this breed, there is no effect of the BMPRIB gene on litter size. Results of some studies, however, indicate there is a significant association between the BMPRIB gene polymorphism and litter size of Tan sheep. The results of the present study, therefore, need to be assessed in future studies due to the very small sample size used for evaluations in the present study (only one individual with BB genotype; Ma and Yu, 2017). The results of the present meta-analysis study indicate that some other molecular markers for the breeding of Tan sheep may need to be evaluated, such as the BMP15, GDF9 genes and others.

5. Conclusions

The effects of BMPRIB gene on litter size are remarkably consistent in many sheep populations of China with each gene copy being associated with an increase in litter size of 0.4 to 0.5 lambs, apart from some populations in which there is not an effect of this gene with the second copy (e.g., Zeller black sheep). Furthermore, there were no effects of the BMPRIB gene on the litter size in the Tan sheep and animals resulting from crossbreeding with this breed. In conclusion, the results from conducting the present meta-analysis study allowed for summarization of the magnitude of BMPRIB gene effects on litter size of sheep populations in China, and the results provide reference information for indigenous sheep breeding programs.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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References

Bangert-Drowns, Robert, L., 1986. Review of developments in meta-analytic method. Psychol. Bull. 99 (3), 388–399.
Berlin, B.J.A., 1988. Publication bias: a problem in interpreting medical data. J. R. Stat. Soc. Ser. A 151 (3), 419–463.
Brockwell, S.E., Gordon, I.R., 2001. A comparison of statistical methods for meta-analysis. Stat. Med. 20 (6), 825–840.
Counsell, C., Fraser, H., 1995. Identifying relevant studies for systematic reviews. BMJ. 310 (6972) 126-126.
Chen, X.Y., Sun, H.X., Tian, S.J., Guo, W.T., 2015. Association of BMPR1B gene with litter size trait and genetic variations in different generations of Hanper Mutton sheep. J. Agr. U. Hebei 38 (2), 99–102.
Chen, Y., Luo, Q., Li, D., Zhang, Y.J., Yang, F.Y., Yang, J.Q., Zhu, W.Y., 2008. Relationship between BMPR-IB polymorphism and litter size in six breeds or strains of sheep. J. Xinjiang. Agr. Univ. 31 (2), 12–16.
Chu, M.X., Jia, L.H., Zhang, Y.J., Jin, M., Chen, H.Q., Fang, L., Di, R., Cao, G.L., Feng, T., Tang, Q.Q., Ma, Y.H., Li, K., 2011. Polymorphisms of coding region of BMPR-IB gene and their relationship with litter size in sheep. Mol. Biol. Rep. 38 (6), 4071–4076.
Chu, M.X., Liu, Z.H., Jiao, C.L., He, Y.Q., Fang, L., Ye, S.C., Chen, G.H., Wang, J.Y., 2007. Mutations in BMPRIB and BMP15 genes are associated with litter size in Small Tailed Han sheep (Ovis Aries). J. Anim. Sci. 85 (3), 598–603.
Der Simonian, R., Laird, N., 1986. Meta-analysis in clinical trials. Control. Clin. Trials 7 (3), 177–188.
Dickersin, K., 1997. How important is publication bias? A synthesis of available data. AIDS Educ. Prev. 9 (1 Suppl), 15–21.
Doi, S.A.R., Barendregt, J.J., Khan, S., Thalib, L., Williams, G.M., 2015. Advances in the meta-analysis of heterogeneous clinical trials I: the inverse variance heterogeneity model. Contemp. Clin. Trials 45 (Pt A), 130–138.
Egger, M., Smith, G.D., Schneider, M., Minder, C., 1997. Bias in meta-analysis detected by a simple, graphical test. BMJ. 315 (7109), 629–634.
Fang, D., Wu, J.P., Xu, J.F., Luo, Y.R., Zhang, L.P., Wang, L., Yang, L., Lei, Z.M., 2010. Research on application effect in breeding of molecular marker in sheep BMPR-

IB gene. Xinjiang. Agr. Sci. 47 (1), 189–194.
Fogarty, N.M., 2009. A review of the effects of the Booroola gene (FecB) on sheep production. Small Rumin. Res. 85 (2-3), 75–84.
Galloway, S.M., Mcnatty, K.P., Cambridge, L.M., Laitinen, M.P., Juengel, J.L., Jokiranta, T.S., McLaren, R.J., Luiro, K., Dodds, K.G., Montgomery, G.W., Beattie, A.E., Davis, G.H., Ritvos, O., 2000. Mutations in an oocyte-derived growth factor gene (BMP15) cause increased ovulation rate and infertility in a dosage-sensitive manner. Nat. Genet. 25 (3), 279–283.
Gholibeikifard, A., Amin Afshar, M., Hosseinpour Mashhadi, M., Mohammadi, H., 2014. Molecular study on the exon 2 region of the ovis bone morphology protein 15 (BMP-15) gene in Iranian Bluchi sheep breed by PCR-SSCP technique. Iran. J. Appl. Anim. Sci. 4 (4), 769–773.
Guan, F., Liu, S.R., Shi, G.Q., Yang, L.G., 2007. Polymorphism of FecB gene in nine sheep breeds or strains and its effects on litter size, lamb growth and development. Anim. Reprod. Sci. 99 (1-2), 44–52.
Hatala, R., Keitz, S., Wyer, P., Guyatt, G., 2005. Tips for learners of evidence-based medicine: 4. Assessing heterogeneity of primary studies in systematic reviews and whether to combine their results. CMAJ 172 (5), 661–665.
Higgins, J.P.T., Thompson, S.G., 2002. Quantifying heterogeneity in a meta-analysis. Stat. Med. 21 (11), 1539–1558.
Higgins, J.P.T., Thompson, S.G., Deeks, J.J., Altman, D.G., 2003. Measuring inconsistency in meta-analyses. BMJ. 327 (7414), 557–560.
Kang, X.L., Liu, J.L., Liu, Y.Q., Wang, S.Y., Feng, D.Z., 2017. Association between BMPR-IB polymorphism and litter size in two sheep groups. Acta. Agr. Bor. Occ. Sin. 26 (4), 497–502.
Khodabakhshzadeh, R., Mohammadabadi, M.R., Esmailizadeh, A., Moradi Shahrebabak, H., Bordbar, F., Ansari Namin, S., 2016. Identification of point mutations in exon 2 of GDF9 gene in Kermani sheep. Pol. J. Vet. Sci. 19 (2), 281–289.
Li, D., Sun, W., Ni, R., Zhang, X.N., Zhang, Y.L., Chu, M.X., Zhang, Y.F., Shen, G.Z., Chen, L., Wu, W.Z., Zhou, H., Han, F., Xu, H.S., 2012. Genetic diversity of FecB gene and association analysis of its litter size. J. Anim. Sci. Vet. Med. 31 (2), 1–5.
Ma, L.N., Yu, Y., 2017. Correalation analysis between Fecundity gene (FecB) SNP genotyping by TaqMan probe and litter size in Tan sheep. Anim. Husb. Feed. Sci. 38 (3), 20–22.
Moghadaszadeh, M., Mohammadabadi, M.R., Esmailizadeh, A.K., 2015. Association of exon 2 of BMP15 gene with the litter size in the raini cashmere goat. Genet. 3rd Millennium 13 (3), 4062–4067.
Mohammadabadi, M.R., Esfandyarpoor, E., Mousapour, A., 2017. Using inter simple sequence repeat multi-loci markers for studying genetic diversity in kermani sheep. J. Res. Dev. 5 154-154.
Mohammadabadi, M.R., Sattayimokhtari, R., 2013. Estimation of (co) variance components of ewe productivity traits in Kermani sheep. Slovak. J. Anim. Sci. 46 (2), 45–51.
Mousavizadeh, A., Abadi, M.M., Torabi, A., Nassiri, M.R., Ghiasi, H., Koshkoieh, A.A., 2009. Genetic polymorphism at the growth hormone locus in Iranian Talli goats by polymerase chain reaction-single strand conformation polymorphism (PCR-SSCP). Iran. J. Biotechnol. 7 (1), 51–53.
Mulsant, P., Lecerf, F., Fabre, S., Schibler, L., Monget, P., Lanneluc, I., Pisselet, C., Riquet, J., Monniaux, D., Callebaut, I., Cribiu, E., Thimonier, J., Teyssier, J., Bodin, L., Cognie, Y., Chitour, N., Elsen, J.M., 2001. Mutation in bone morphogenetic protein receptor-IB is associated with increased ovulation rate in Booroola Merino ewes. P. Natl. A. Sci. 98 (9), 5104–5109.
Nicol, L., Bishop, S.C., Pong-Wong, R., Bendixen, C., Holm, L.E., Rhind, S.M., McNeilly, A.S., 2009. Homozygosity for a single base-pair mutation in the oocyte-specific GDF9 gene results in sterility in Thoka sheep. Reproduction 138 (6), 921–933.
Pan, Z.Y., Zhang, B.Y., Hu, W.P., Di, R., Lin, Q.Y., Wang, X.Y., Yin, D.H., Wang, P.Q., Chu, M.X., 2015. The genetic diversity of both FecB gene and microsatellite GC101 is associated with reproduction selection in sheep. Turk. J. Vet. Anim. Sci. 39, 254–260.
Ren, Y.L., Shen, Z.Q., LI, M., Xiao, N., Dong, W.Y., Li, J.L., Wang, J.J., 2011. Association of polymorphisms in the FecB gene with litter size in Wadi sheep. China. Anim. Hus. Vet. Med. 38 (7), 159–162.
Rosenthal, R., Rubin, D.B., 1982. Comparing effect sizes of independent studies. Psychol. Bull. 92 (2), 500–504.
Seidenfeld, J., Piper, M., Bohlius, J., Weingart, O., Trelle, S., Engert, A., Skoetz, N., Schwarzer, G., Wilson, J., Brunskill, S., Hyde, C., Bonnell, C., Ziegler, K.M., Aronson, N., 2006. Comparative effectiveness of epoetin and darbepoetin for managing anemia in patients undergoing cancer treatment. AHRQ. 68 (4), 281–282.
Shao, Y.G., Mirinisahan, K., Liu, W.J., 2012. Study on the relationship between the polymorphism of BMPR-IB gene and litter size in Xinjiang cele black sheep. China. Anim. Hus. Vet. Med. 39 (6), 221–223.
Shi, H.C., Gao, Z.Y., Niu, Z.G., Bai, J., Feng, L.J., Li, H.B., Jia, B., Zhang, Y., 2011. Detection of FecB mutation and its relationship with litter size in Xinjiang Duolang sheep (Ovis Aries). J. Agric. Biotechnol. Sustain. Dev. 19 (2), 330–334.
Shi, H.C., Niu, Z.G., Bai, J., Feng, L.J., Mu, M.R.S., Yang, Q.Y., Liu, M.J., Jia, F., 2012. Effect on litter size of Cele black sheep and genetic regularity of BMPR-IB gene mutation. China. J. Anim. Sci. 38 (3), 14–17.
Soufy, B., Mohammadabadi, M.R., Shojaeyan, K., Baghizadeh, A., Ferasaty, S., 2009. Evaluation of Myostatin gene polymorphism in Sanjabi sheep by PCR-RFLP method. Anim. Sci. Res. 19 (1), 81–89.
Sterne, J.A.C., Sutton, A.J., Ioannidis, J.P.A., Terrin, N., Jones, D.R., Lau, J., Carpenter, J., Rücker, G., Harbord, R.M., Schmid, C.H., Tetzlaff, J., Deeks, J.J., Peters, J., Macaskill, P., Schwarzer, G., Duval, S., Altman, D.G., Moher, D., Higgins, J.P., 2011. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ. 343, d4002.
Sun, H.X., Dun, W.T., Chen, X.Y., Tian, S.J., Tan, W., 2011. Relationship between polymorphism of BMPR-IB gene and litter size and sexual season for different sheep breeds. Hunan Agric. Sci. Technol. 3, 147–149.
Tian, X.E., Sun, H.X., Wang, Y.J., 2009. Genetic polymorphism of BMPR-IB gene and effect on litter size in three sheep breeds. J. Northwest. F. U-Nat. Sci. Edit. 37 (11), 31–36.
Topol, E.J., Califf, R.M., 1992. Answers to complex questions cannot be derived from “simple” trials. Brit. Heart. J. 68 348-348.
Vajed Ebrahimi, M.T., Mohammadabadi, M.R., Esmailizadeh, A.K., 2016. Using microsatellite markers to analyze genetic diversity in 14 sheep types in Iran. Arch. Anim. Breed. 60 (3), 183–189.
Wang, W.M., Liu, S.J., Li, F.D., Pan, X.Y., Li, C., Zhang, X.X., Ma, Y.J., La, Y.F., Xi, R., Li, T.F., 2015. Polymorphisms of the Ovine BMPR-IB, BMP-15 and FSHR and their associations with litter size in two chinese indigenous sheep breeds. Int. J. Mol. Sci. 16, 11385–11397.
Wang, X., Maimaitiyiming, B.L.T., 2010. Studies of BMPR-IB gene as a candidate gene for prolificacy in Duolang Sheep. Xinjiang. Agr. Sci. 47 (9), 1813–1818.
Wei, L.J., Dong, H.J., 2006. The identification and solution of heterogeneity in Meta-analysis. Acad. J. Sec. Mil. Med. Univ. 27 (4), 449–450.
Wilson, T., Wu, X.Y., Juengel, J.L., Ross, I.K., Lumsden, J.M., Lord, E.A., Dodds, K.G., Walling, G.A., McEwan, J.C., O’Connell, A.R., McNatty, K.P., Montgomery, G.W., 2001. Highly prolific Booroola sheep have a mutation in the intracellular kinase domain of bone morphogenetic protein IB receptor (ALK-6) that is expressed in both oocytes and granulosa cells. Biol. Reprod. 64 (4), 1225–1235.
Wozney, J.M., Rosen, V., Celeste, A.J., Mitsock, L.M., Whitters, M.J., Kriz, R.W., Hewick, R.M., Wang, E.A., 1988. Novel regulators of bone formation: molecular clones and activities. Science 242 (4885), 1528–1534.
Yang, H., Yang, Y.L., Liu, S.R., Zhong, F.G., Zhang, Y.S., He, Q.H., 2010a. Analysis of single nucleotide polymorphism of BMPR-IB gene in sheep. Acta. Agr. Bor. Occ. Sin. 19, 7–11.
Yang, J., Zheng, Q.S., 2005. Statistical methods of meta-analysis. Chinese. J. Clin. Pharmacol. Ther. 10, 1309–1314.
Yang, Y.Y., Tian, Y., Da, L., Cao, G.F., Shao, K., Su, H., Qing, G.L., Wu, D.B.L., Zhou, X., 2010b. Study on the BMPR-IB gene as candidate gene for fecundity in Mongolian sheep double-lambs group. Heilongjiang. Anim. Sci. Vet. Med. 11, 1–4.
Yang, Y.Z., Feng, T., Chu, M.X., Yun, P., Xiao, W., Xue, Z.H., Zhang, J.T., Meng, D.N., 2012. Fec^{B} mutation of BMPR-IB gene and its association with litter size and growth traits in small tailed han sheep. Acta. Agr. Bor. Occ. Sin. 27 (5), 38–43.
Zamani, P., Akhondi, M., Mohammadabadi, M.R., 2015. Associations of Inter-Simple Sequence Repeat loci with predicted breeding values of body weight in sheep. Small Rumin. Res. 132, 123–127.
Zhu, E.Y., Shi, H.C., Wu, J., Liu, M.J., Jian, Z.J., Bai, J., Xu, X.M., 2006. Study on bone morphogenetic protein receptor IB as a candidate gene for prolificacy in sheep. Acta. Agr. Bor. Occ. Sin. 15, 20–23.