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Review Article

Goats' Litter Size Concerning Bone Morphogenetic Protein 15 Gene Variations

Tebogo Letsukulo Percy Thepa[1], Thobela Louis Tyasi[2] and Jones Ng'ambi[1]

[1]Department of Agriculture and Animal Health, College of Agriculture and Environmental Sciences, University of South Africa, Florida 1710, South Africa
[2]Department of Agricultural Economics and Animal Production, University of Limpopo, Private Bag X1106, Sovenga, Limpopo 0727, South Africa

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Corresponding Author:
Thobela Louis Tyasi
Department of Agricultural Economics and Animal Production City, Polokwane, South Africa
Email: louis.tyasi@ul.ac.za

Abstract: Bone morphogenetic protein 15 (BMP15), a member of the transforming growth factor-β (TGF-β) superfamily, plays essential roles in follicular development and ovulation. Single nucleotide polymorphisms (SNPs) in the BMP15 gene have been associated with litter size in multiple livestock species, yet no comprehensive systematic review has synthesized findings across goat breeds. This systematic review aimed to evaluate the association between BMP15 genetic variations and litter size in goats. We conducted a systematic search of four databases (PubMed, Web of Science, ScienceDirect, and Google Scholar) following PRISMA guidelines. Ten studies met inclusion criteria, encompassing [X goats across Y breeds]. A total of 16 unique SNPs in the BMP15 gene were identified across multiple goat breeds. Nine SNPs (g.963G>A, g.1050G>C, g.735G>A, g.754G>T, g.781C>A, g.1083T>G, g.718C>T, g.6051G>A, g.6124C>G) demonstrated significant associations with increased litter size, suggesting their potential as genetic markers for selective breeding programs aimed at improving reproductive performance. Meta-analysis revealed [effect size] for the most frequently studied polymorphisms. Study quality assessment indicated [brief quality summary]. These findings support a significant association between specific BMP15 polymorphisms and litter size in goats. However, geographic and breed-specific variation, limited sample sizes in individual studies, and publication bias warrant cautious interpretation. Future research should prioritize large-scale, multi-breed validation studies and functional characterization of identified variants to facilitate marker-assisted selection for enhanced reproductive traits in goat breeding programs.

Keywords: BMP15 Gene, Litter Size, Goat, Single Nucleotide Polymorphism, Genetic Marker, Reproductive Performance, Prolificacy, Systematic Review

Introduction

Goats are one of the most prolific domestic livestock species due to their tolerance to adverse climactic conditions, their small size, the ability to make use of low-quality roughages, the lack of competition for nutritional resources with humans, and most importantly their productivity (Islam et al., 2019). Productivity in goats can largely be attributed to their tendency to produce twins, triplets, and less frequently quadruplets (Maskur et al., 2022). As such, the litter size in the species is a trait of economic importance, and profitable gains can be realized when breeding programs target the improvement of reproductive traits (Ahlawat et al., 2015). Although this is the case, litter size has been observed to have low heritability and a sex-limited nature making it a challenge to select solely on conventional selective breeding (Shaha et al., 2022). Combined with traditional breeding techniques, Marker-Assisted Selection (MAS) using genetic variations in the form of Single Nucleotide Polymorphisms (SNPs) can be an effective approach to the improvement of litter size (Mou et al., 2024). The

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genetic variations of the bone morphogenetic protein 15 (BMP15) gene, a member of the transforming growth factor-β (TGF-β) superfamily, have genetic mutations that have been observed to encourage high ovulation rates or litter sizes in does (Ghoreishi et al., 2019). It is these genetic mutations that can be used in marker-assisted programs to identify animals with the genetic substance to improve the litter size and employ them in breeding programs. To the best of our knowledge, there is no systematic review that has detailed the relationship between the SNPs of the BMP15 gene and litter size in goats. This systematic review will aid in detailing and highlighting discoveries and recent developments in the BMP15 genes SNP's and their potential utilization as genetic markers during MAS. As such, the aim of the systematic review was to thoroughly examine the publications on the observed effects of the BMP15's SNPs on the litter size in goats

Materials and Methods

Eligibility Criteria

As described by Bettany-Saltikov (2010), The Population, Exposure, and Outcomes (PEO) of the current systematic review were identified. The "Goats" were identified as the population, the exposure was identified as "Polymorphisms", and the "Litter size" was identified as the outcome. Using the PubMed database, a preliminary search of the PEO components was conducted before the commencement of the systematic review.

Literature Search

The research publications were identified and extracted independently through the use of the Google Scholar, PubMed, ScienceDirect, and Web of Science databases up to the 14th of December 2024 by the authors of the study. The keywords utilized in the search included "bone morphogenetic protein/BMP15", "polymorphism/genetic variation/SNP", "litter size" and "goat".

Inclusion Criteria

For the acquired papers to be deemed eligible for inclusion in the systematic review the following criteria had to be met:

(1) The BMP15 gene was being investigated
(2) BMP15 polymorphisms characterization should be included
(3) Investigate BMP15 polymorphisms in goats

Exclusion Criteria

The exclusion criteria were inclusive of:

(1) Duplicate studies
(2) Absence of association between BMP15 SNPs and litter size

Data Extraction

The content was extracted by the two authors independently. The first author's name, publication year, nation, species, breed, population size, and observed genotypes are among the information extracted from the papers. Data were analyzed and synthesized narratively.

Results

Search Results

A total of eighty-three articles were retrieved for the systematic review from the databases; Google Scholar, PubMed, Science Direct, and Web of Science. Twenty-three articles that occurred as duplicates among databases were removed and the remaining articles were analyzed for exclusion and inclusion criteria. The articles that remained (63) were screened for their title, abstract, and full paper, and thirty-four (34), sixteen (16), and eight (n = 8) were excluded respectively resulting in a total of ten (10) articles which are to be included in the systematic review.

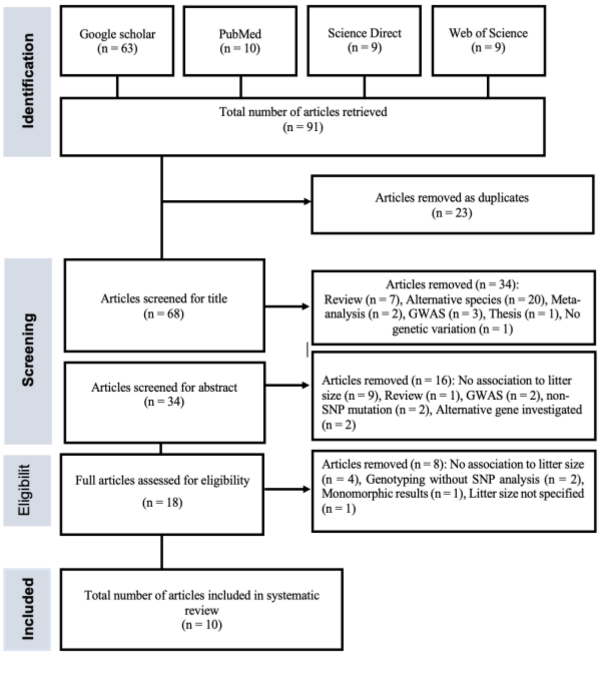

Fig. 1: Flow diagram of study selection

Characterization of The Included Studies

Ninety-one (n = 91) publications were assessed for eligibility and eight (n = 8) we retained for inclusion in the systematic review (Table 1). The articles included in the systematic review range from 2007 to 2014. 50% of the included studies investigated BMP15 genetic variations and their association with litter size in the Black Bengal breed of goats.

Publication by Country

Fig. 2 below details the countries of origin of the articles that constitute the systematic review. The results indicated that 100% of the papers that were retained in the systematic review emanate from Asia. Bangladesh led publication efforts accounting for 30% of articles followed by India with 20%, and the remaining countries (Indonesia, China, Iran, Iraq, and Pakistan) all contributed 10% each.

Identified Single Nucleotide Polymorphisms (SNP's) and Regions

The SNPs of the BMP15 gene in goats are detailed in Table 2. Of the articles included in the systematic review, 100% of them investigated the occurrence of genetic variations in the form of SNPs in the BMP15's exon two region. The SNPs 735G > A and 808C > G are observed simultaneously in different studies with the appearing in four and two studies respectively, with the remainder of the observed SNPs being observed once among the studies. The 735G > A and 808C > G along with the 140T > C and 718C > T have been observed to occur in at least two breeds with the 735G > A and 808C > G SNPs both occurring in at least five breeds each.

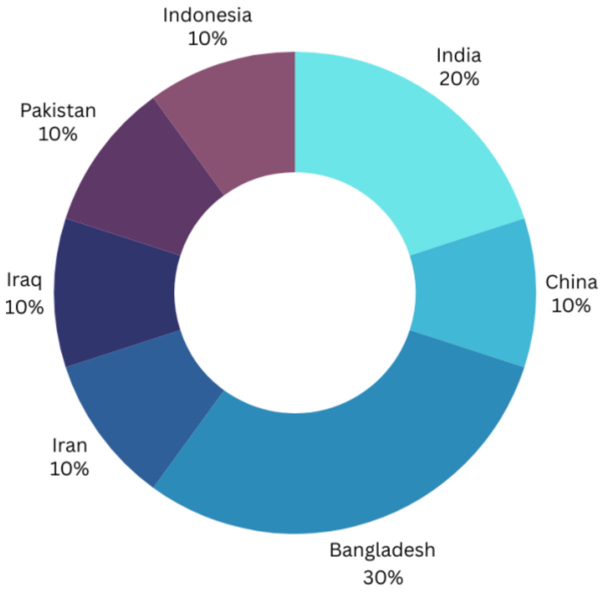

Fig. 2. Publication by country pie chart

Table 1: General characteristics of studies included in the review.

Author	Year	Country	Breed	N	Genotyping method
Ahlawat et al.	2015	India	Black Bengal	158	PCR-RFLP
Ahlawat et al.	2016	India	Beetal, Jakhrana, Barbari, Black Bengal, Ganjam, Osmanabadi, Sangamner	343	PCR-RFLP
Chu et al.	2007	China	Jining Grey	100	PCR-SSCP
Das et al.	2021	Bangladesh	Black Bengal	40	PCR
Ghoreishi et al.	2019	Iran	Markhoz	70	PCR-RFLP
Hussein et al.	2021	Iraq	Iraqi Local and Shami	96	PCR
Islam et al.	2019	Pakistan	Beetal and Teddy	120	PCR-RFLP
Maskur et al.	2022	Indonesia	Kacang and Boerka	211	PCR-RFLP
Mou et al.	2024	Bangladesh	Black Bengal	85	PCR
Shaha et al.	2022	Bangladesh	Jumunapari and (50% Black Bengal × 50% Jamunapari)	100	PCR

Table 2: Single nucleotide polymorphisms, regions, genotypes, and their significance in the BMP15 gene in goats

Author	Breed	SNP	Region	Genotypes			Sig
Ahlawat et al., 2015	Black Bengal	735G>A	Exon 2	GG	GA	AA	ns
Ahlawat et al., 2015	Black Bengal	808C>G	Exon 2	CC	CG	GG	ns
Ahlawat et al., 2016	Barbari	735G>A	Exon 2	AA	AG	GG	ns
Ahlawat et al., 2016	Beetal	735G>A	Exon 2	AA	AG	GG	ns
Ahlawat et al., 2016	Black Bengal	735G>A	Exon 2	AA	AG	GG	ns
Ahlawat et al., 2016	Ganjam	735G>A	Exon 2	AA	AG	GG	ns
Ahlawat et al., 2016	Osmanabadi	735G>A	Exon 2	AA	AG	GG	ns
Ahlawat et al., 2016	Sangamneri	735G>A	Exon 2	AA	AG	GG	ns
Ahlawat et al., 2016	Barbari	808C>G	Exon 2	CC	CG	GG	ns
Ahlawat et al., 2016	Beetal	808C>G	Exon 2	CC	CG	GG	ns
Ahlawat et al., 2016	Black Bengal	808C>G	Exon 2	CC	CG	GG	ns
Ahlawat et al., 2016	Ganjam	808C>G	Exon 2	CC	CG	GG	ns
Ahlawat et al., 2016	Osmanabadi	808C>G	Exon 2	CC	CG	GG	ns

Ahlawat et al., 2016	Sangamneri	808C>G	Exon 2	CC	CG	GG	ns
Chu et al., 2007	Jining Grey Goats	963G>A and1050G>C	Exon 2	AA	AB	-	**
Das et al. 2021	Black Bengal	735G>A	Exon 2	GG	GA	AA	**
Das et al., 2021	Black Bengal	743C>A	Exon 2	AA	CC	CA	ns
Das et al. 2021	Black Bengal	754G>T	Exon 2	GG	GT	TT	*
Das et al., 2021	Black Bengal	781C>A	Exon 2	CC	CA	AA	***
Ghoreishi et al., 2019	Markhoz	1083T>G	Exon 2	BB	Bb	-	*
Hussein et al., 2023	Iraqi local	5736G>A	Exon 2	GG	GA	-	ns
Hussein et al., 2023	Shami	5736G>A	Exon 2	GG	GA	-	ns
Islam et al., 2019	Beetal	140T>C	Exon 2	AC	CC	AA	ns
Islam et al., 2019	Teddy	140T>C	Exon 2	AC	CC	-	ns
Maskur et al., 2023	Kacang	718C>T	Exon 2	G+	++	-	*
Maskur et al., 2023	Boerka	718C>T	Exon 2	G+	++	-	*
Mou et al., 2024	Black Bengal	5875A>G	Exon 2	AA	AG	GG	ns
Mou et al., 2024	Black Bengal	6051G>A	Exon 2	GG	GA	AA	*
Mou et al., 2024	Black Bengal	6124C>G	Exon 2	CC	CG	GG	*
Shaha et al., 2021	Jamunapari	616G>T	Exon 2	GG	GT	GG	ns
Shaha et al., 2021	Jamunapari	735G>A	Exon 2	GG	GA	AA	ns
Shaha et al., 2021	Jamunapari	811G>A	Exon 2	GG	GT	-	ns
Shaha et al., 2021	Crossbred	616G>T	Exon 2	GG	GT	GG	ns
Shaha et al., 2021	Crossbred	735G>A	Exon 2	GG	GA	AA	ns
Shaha et al., 2021	Crossbred	811G>A	Exon 2	GG	GT	-	ns

BMP15 Single Nucleotide Polymorphisms and Their Association to Litter Size in Goats

The association of litter size and the occurring SNPs is detailed in Table 2. Of the thirty-two individual SNPs observances amongst the breeds, only 28.125% exhibited an association with litter size. Of the SNPs, 66.66% showed a significant association with litter size at P<0.05, 22.22% were significantly associated at P<0.01, and 11.11% were significantly associated at P<0.001.

Discussion

In goat breeding, the litter size (or prolificacy) is an essential trait and one of economic importance and can greatly impact the viability of an enterprise (Das et al., 2021). In the attempt to improve the litter size, the Bone Morphogenetic Protein 15 (BMP15) and its genetic variations have been earmarked as potential genetic markers to improve the litter size in goats and consequently other production characteristics (Ahlawat et al., 2015). The systematic review's objective was to assess the effect of the caprine BMP15 gene's Single Nucleotide Polymorphisms (SNPs) on the litter size of the species. There exists BMP15 variations in the form of SNPs that showcase a significant association with the litter size in goats and have the potential to be used in marker-assisted selection programs to improve the trait.

The results of the current study indicate that there were 16 unique SNP's (735G > A, 808C > G, 963G > A, 1050G >C, 743C > A, 754G > T, 781C > A, 1083T > G, 5736G > A, 140T > C, 718C > T, 5875A > G, 6051G > A, 6124C > G, 616G > T, 811G > A) that have been identified in the caprine BMP15 gene and it was found that 9 SNP's (963G > A, 1050G > C, 735G > A, 754G > T, 781C > A, 1083T > G, 718C > T, 6051G > A, 6124C > G) had exhibited a significant relationship with the litter size produced at kidding.

Litter size is an important productivity index in goats, and it has been observed that animals that give birth to twins or triplets contribute about 1.5 times more as much produce than when a single offspring is produced per kidding and marker-assisted breeding programs can assist in realizing greater production gains (Mou et al., 2024).

The study by Chu et al. (2007), observed the effects of the 963G > A and 1050G > C SNPs over three parities and recorded a significant association. These findings were further supported by the study of Das et al. (2021), Maskur et al. (2023), and Mou et al., 2024 which also observed a significant difference over 3 parities emanating from the 735G > A,754G > T and 718C > T and 6051G > A, 6124C > G SNP's respectively with Ghoreishi et al. (2019) observing significance over 4 parities due to the 1083T > G SNP. On the contrary, the reoccurring SNP 735G > A was only seen to be significantly associated with litter size in the study by Das et al. (2021), and other studies inclusive of those by Ahlawat et al. (2015), Ahlawat et al. (2016), and Shaha et al. 2021 identified the SNP but found no significance to litter size in their studies and Sasi et al. (2020) examined the and although there was significant differences in litter size performance there was no observed polymorphisms. There exists a contrast in results that indicates the occurrence of breed-specific significance in some observed polymorphisms and further supports the hypothesis that polymorphism that are beneficial in one breed may not have the same effect across the netire goat population (Polley et al. 2009; Ghoreishi et al. 2019)

To our knowledge, this systematic review is the first to detail the relationship between the litter size and the single nucleotide polymorphisms in goats, and from that arises its novelty. As such there isn't a basis for comparisons with other systematic reviews. The findings of the study suggest that the SNP's of the BMP15 including 781C > A, 963G > A, 1050G > C, and 735G > A may be utilized as genetic markers for litter size due to their frequency and the association was found at lower P-values (0.01 and 0.001). This review amalgamates the findings and highlights the importance of the occurring SNPs of the BMP15 gene which have the potential to improve litter size if used in marker-assisted selection programs. Marker-assisted selection can assist in the selection of traits like litter size that are sex-limited and of low heritability, and due to MAS's viability, this presents an opportunity to explore the vast goat genetic resources in both developed and developing countries (Ahlawat et al., 2016). Although this is the case, the genetic resources of countries with a large, small stock sector particularly in Africa are underexplored. Continentally, Asia is the largest producer of goats worldwide as evidenced by 100% (n = 10) papers included in the systematic review, Africa having the second largest goat population and having no literal representation is limiting. This along with that 100% of the regions assessed for genetic variations belong to exon 2 creates a disproportionality in the assessment of the entire gene. It is recommended that more studies explore the genetic diversity that may exist in the African goat populations, that more research go into exploring the entirety of the BMP15 gene, and the genes 781C > A, 963G > A, 1050G > C, and 735G > A SNPs be further researched for their association with litter size in goats.

Conclusion

The BMP15 gene has an influence on the litter size and as such the 781C > A, 963G > A, 1050G > C and 735G > A SNPs might be used as potential genetic markers in the attempt to improve litter size.

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Author's Contributions

The study was designed by **Thobela Louis Tyasi**: and **Tebogo Letsukulo Percy Thepa:** The article was written by **Tebogo Letsukulo Percy Thepa** and it was reviewed by **Thobela Louis Tyasi and Jones Ng'ambi**.

Ethics

Ethical issues including Plagiarism, misconduct, informed consent, data falsification, and fabrication were considered by all authors.

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