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Association of growth differentiation factor 9 and bone morphogenetic protein 15 gene expression with litter size and growth traits in ewes

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Abstract*— Breeding symptoms in sheep (ovis aries) are complicated, many genes affected by genes and environmental factors, as well as influenced by interaction between them. The polymorphisms in many genes associated with reproductive symptoms have been recorded in breeds by many sheep worldwide. Breeding symptoms significantly affect the profitability of lamb cultivation, which is eventually expressed in the number of lambs per lamb. Since most events only produce a lamb due to low reproductive efficiency or poor genetics, it is of great scientific and economic importance to identify genes responsible for specific reproductive symptoms. Ovulation is a complex mechanism that varies between species and depends on genetic and environmental factors. Mammals can have either mono-convulatory or poly-convulatory, which may be based on the number of eggs released during ripe and ovulation. The BMP system is an important ovary regulatory system, which plays an important role in the mechanism responsible for choosing follicles in large household species. Development of follicle in the ovaries of mammal species is strongly influenced by different BMPs, so we recognize the importance of assessing these factors, which play an important role in affecting ovulation, coup discrimination and cumulous expansion. The BMP family has more than 30 members, with BMP15 most important. Development discrimination factor 9 (GDF9) gen is an important breeding gene studied in many sheep. The polymorphisms in these genes have shown significant relationships with fertility symptoms such as ovulation speed and garbage size and have been used in reproductive programs. The transforming growth factor Beta (TGF-β) Different mutations in the GDF9 genes in the family have been shown to affect the fertility of the sheep. Increasing garbage size is important for the profitability of sheep production, but it is just one of the several factors that makes lamb cultivation profitable. In the sheep, genetic variation in the size of the garbage and ovulation speed is widely documented, and many conclusions have indicated sufficient differences between the breeds and within different mechanisms. Given that breeding symptoms have less heredity, and the selection is slow and disabled depending on phenotype values, the purpose of this study is to examine the relationship between genes and these symptoms, which emphasizes the relationship between polymorphism in GDF9 and BMP15.

***Keywords* — GDF9 gene; BMP15 gene; litter size; reproduction; fecundity genes.**

INTRODUCTION

Gets (*Ovis Aries*) were among the most important economic animals in the world. He played an important role in agriculture, economics and culture in the first days of human civilization. It made the sheep one of the most successful animals of humans in the early Neo - Fate (Jhao *et al*., 2023). Several studies have shown that performance of the nesting system is affected by genetic diversity. The discovery of gene polymorphism can provide potential molecular genetic markers for sheep breeding (2).The Saubilen takes the *BMP15* genes on the chromosome, and GC has shown that *BMP15* prevents progesterone production stimulated by a follicle stimulating hormone (FSH) without affecting estradiol. BMP15 -POLIMORFISM affects ovarian function, garbage size and reproduction in cattle, and *BMP15* is considered an important gene affecting reproduction in cattle.Growth Factor Discrimination 9 (*GDF9*) is related to the transforming growth factor Beta (*TGF -ß*) family (3).

The *GDF9* is expressed in the ovaries, stimulates the development of the follicle, promotes granulosa cell proliferation, affects the cell's vitality signaling route and controls other growth factors and hormones (4). The *GDF9* is shown to play a role as an external factor excreted by oocytes and is an external factor in Granulosa cells (5). The *GDF9* genes also affect transgembren receptor protein sanes (SRP) and include ovulation cycle, coupling production and gonadal development (6). The *GDF9* genes in the sheep are located on the chromosome 5 and have two exones and 1,126 base pairs spread. The long maturity peptide of this gene consists of 135

amino acids, while preppide consists of 453 amino acids (7). Coded Preprotein encounters a factor required for folliculogenesis in the ovaries. This factor stimulates granulosa cell growth and promotes the development of primardial follicles (8).The *GDF9* gene in oocyte controls several enzymes in granulosa cells, which is responsible for ovulation, fertilization and successful reproduction. Deletion of the *GDF9* genes has been shown to reduce follicular development and food infertility (9). The *GDF9* is important for breeding work in Gener Ewes (10). The gene has an important role in granulosa, cumylas and trapping cells, which promote folliculogenesis, ozogenesis and ovulation, contribute to female fertility (11). Therefore, all knowledge of the work of these markers is useful for breeders to improve the ovulation speed and garbage size of cattle (12).

Effect of the *GDF9* and *BMP15* gene on litter size.

Given the synergistic role of *BMP15* and *GDF9* in oocyte development, ovulation regulation, and follicle production, any changes in the *BMP15* gene codon may result in a less biologically active and mature protein with abnormal binding to GDF9, negatively impacting the ovarian response to ovulatory stimulation (13). The *BMP15* is also known as *GDF9β*. Both *BMP15* and *GDF9* genes belong to the transforming increase component β (*TGF-β*) family (14). Figure 1 suggests that each GDF9 and BMP15 bind through BMPR1 to transmit alerts to cells. The *GDF9* and *BMP15* can shape homodimers or integrate to form heterodimers. GDF9-BMP15 heterodimers could have precise physiological capabilities. Both *GDF9* and *BMP15* may also exhibit aggressive inhibition (15). Therefore, some studies have counseled that the ratio of these two genes determines clutter size (LS) (16). Di et al. (2021) (17) suggested that *BMP15* is a essential gene for clutter length in Lochong sheep, and that those 4 SNPs might be used as candidate variables to enhance clutter size. The effects propose an interactive impact among *BMP15* and *FecB/GDF9* in influencing clutter size.

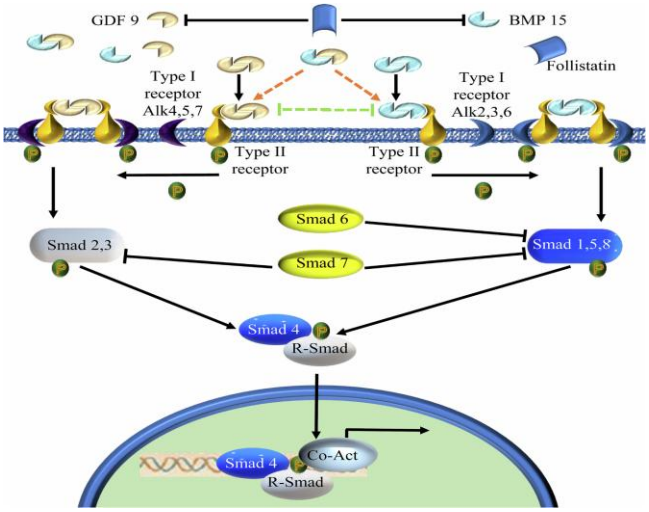

Fig. 1. Cross -stock mode between GDF9 and BMP15 Signaling.

Benmorfozenic protein 15 (BMP15) first binds the bone morphogenate protein receptor 2 (BMPR2) to the form complex. Then the complex is recognized and bound by BMPR1B (ALK6) which activates Thesmad1/5/8 signaling pathway. Phosphere binds SMAD1/5/8 SMAD4 and enters the core to interfere with translation and translation. Development discrimination factor 9 (GDF9) includes the same route, and signal transmission takes place through BMPR1B (ALK 5) and SMAD2/3. GDF9 and BMP15 Signaling can stop each other (18).

SNP Loki is important benchmarks for reproductive variants, as they are an important factor in molecular markers - based breeding of sheep. The previous study indicated that not all mutations in the *GDF9* genes change LS. Mutation located in introns has no effect, while people located in the promoter region to a large extent affect LS (19). Of course, there are some mutations in exon, but they do not change the amino acid sequence (20). Many studies have indicated a significant impact of *BMP15* and *GDF9* genes on breeding symptoms in sheep. These genes are called prime candidate genes for breeding in sheep (4). Reproductive symptoms, finally expressed as lamb of lamb per lamb, largely affect the profitability of sheep cultivation, as most events normally only produce one lamb in Iraqi events. Marzanov *et al.* (2023) (21) studied polymorphism in specific Loki, which is known for affecting some breeds, but does not always guarantee positive results in other breeds. In contrast, Deniskova et al. (2023) (4), These SNPs vary greatly between lamb with high and low power. Candidates for most reproductive symptoms are mainly reproductive genes, such as BMP15 (bone morphogennetic protein 15), *GDF9* (growth discrimination 9) (22), and BMPR 1B (Benmorphological Protein Protein receptor type 1B).

Development of follicle in the ovaries of mammal species is significantly affected by different BMPs, as shown in recent studies by Sarma et al. (2019) (23), Kumar et al. (2020) (24), Ali et al. (2022) (25), and Imran and Al-Tuwani (2024) (26).

These studies recognize the importance of assessing these factors, as they play an important role in affecting ovulation, follicular discrimination and cumulous extension. Hormonal input and growth factor, including bone morphogenetic protein (BMP), plays an important role in this process (24).The BMP transforming growth factor-oil (TGF-β) is a member of the family, who plays a role in the development of ovaries (27).

Role of GDF9 and BMP15 in ovary

The primary regulatory capacity of the oocyte for follicular growth and discrimination is achieved through synthesis and secretion of specific oocyte factors, especially paragorine factor *GDF9* and *BMP15*, which directly serves through direct physical contact in granulosa cell border interface. Granulosa -cells (GCS) and Cumylas cells (CC) play an essential role in the OOCT maturity, follicular development and maturity, ovulation and fetal development around the OOCT. BMP is shown to regulate folkulogenesis in mammals (28). Granulosa -cells (GCS) and Cumylas cells (CC) play an essential role in the OOCT maturity, follicular development and maturity, ovulation and fetal development around the OOCT. Oocyte and cumulus cells form cumulus-Oocyte complex (COC) and maintains wide Bupy communication. The Commulus protein is shown to regulate folkulogenesis in mammals (28). Cumulus proteins are important because of their important role in follicular development and discrimination, Cumyla's follicle expansion and ovulation (29).

The spread of granulosa or cumulus cells and cell death is closely linked to follicular growth and development. The BMP family development factors have the largest of the TGF-off family, and there are many tasks in modifying cell proliferation, discrimination and existence. Originally, BMP4 was recognized for its role in promoting cartilage and bone formation, but now BMP is shown to regulate the development of teeth, kidneys, skin and muscles (28).The growth and development of the ovaries is regulated by BMP with a spatial and tissue -specific pattern. Of these, BMP2, BMP5 and BMP6 have been expressed in oocytes in Kim cells, BMP6 and BMP15, and BMP2, BMP4 and Theca cells in BMP7. MRNA expression of BMP4 was examined in cattle, sheep, mice, mice and ovarian follicle cells. For Bovine secondary Rome improved supplements with BMP4 in cultural medium improved follicle development and entral formation. In in vitro-recommended human embryos weakened BMP4 joint formation of blastocysts and induced apoptosis in blastocysts. Overall, BMP4 is included in follicular development and female fertility (28).

Effect of the *GDF9* and *BMP15* gene in Growth traits in ewes.

Development symptoms are good indicators of the adaptability of an animal for current environmental conditions and are crucial to production, reproduction and survival. The rapid growth rate eventually determines the meat production capacity of the marketing age, so the selection is used as a criterion. They are largely influenced by genetic and non-genetic factors and interactions between them. It improves these symptoms when using direct phenotype selection using disabled and time -consuming. In addition, most of these symptoms have less heredity, gender -specific, and appear later in life, making them difficult to determine volume in young animals and use direct selection on symptoms. For this reason, and with progress in molecular genetics and sequencing technologies, researchers from all over the world have discovered several candidate genes associated with reproductive symptoms in different sheep. It asks to identify the genetic base of reproductive symptoms and includes them in selection decisions to improve the breeding performance in sheep delays.

Genetic Factors Affect in Growth Traits.

Symptoms of development are strongly affected by various environmental factors, such as sex, garbage types (single or twins), mother's weight, birth and year. Therefore, it is necessary to know the exact estimates of genetic and phenotype parameters for performance symptoms to develop appropriate selection strategies to achieve genetic improvements for these symptoms. The estimate of heredity is useful in the construction of the selection indices, predicting genetic reaction to selection and determine the extent to which a person's phenotype can rely on in selection. Therefore, accurate heredity for various economic symptoms is indispensable in animal breeding programs.

Effect of the *BMP15* gene in Growth traits in ewes.

Tang et al., (2018) (30), demonstrated that the EV -which bears FECB mutation had a high ovulation rate, which may be responsible for the low expression of *BMP15* in the ovarian to the Bibi Sea. However, some studies have also concluded that the *BMP15* is an important gene in the goat's fertility, indicating that the *BMP15* expression in the Harkinian ovaries was much higher in multi-tender stress than the *BMP15* expression Simple-Jede Stress (31). Getmantseva et al in studies (2019) (32) shows a multilateral analysis of the variance a very statistically important impact of the *GDF9* gene SNP on the lamb's birth weight. As a result, the weight of the birth of lambs in EVS of the AG genotype was found to be 0.156 kg more than the roof beard on the GG gene. Many factors significantly affect birth weight, including calving types, nutrition, race and sex. Although this study did not assess the nutritional status of mothers, but the birth weight observed within the specific area indicates that mothers were well cared for during pregnancy. Torres et al. (2021) (33) It was exposed as an important aspect of production systems that may affect the results.

Effect of the *GDF9* gene in Growth traits in ewes.

The gene that encodes growth hormone (GH) and growth differential factor 9 (GDF9) has been proposed as a potential candidate genes affecting total muscle mass growth and, as a

result, such as a result, meat productivity (34). Sarsk's Onlers have many data on the effect of different genetic variations of GDF9 genes on the living weight of short sheep, as well as on the yield of AFSI short sheep's milk, the ability to study polymorphisms and suggest their relationship with the ability to study polymorphisms and meat productivity indicators.Al-Khajai and Ahmed (2019) (35) studied associations between *GDF-9* genes and milk production symptoms. He examined polymorphisms in the *GDF9* gene/exon-1, and gave genotypes and some milk production and relationships between reproductive symptoms in innovative sheep. The used polymerase chain reaction regulation fluorescence (PCR-RFLP) method to study the ratio of GDF-9-Gen Loki and reproduction and symptoms other than the size of the garbage.

The results showed no statistically significant difference between the *GDF9* genes of the *GDF9* genes during the total milk production and breastfeeding period, indicating that the expression of the *GDF9* genes no effect on proteing milk production and breastfeeding duration as a result of the expression of the *GDF9*, but has effects on other animal symptoms. Jawasra and Ismail (2018) (36) identified the associations in the middle of the polytes in prolactin (PRG), *GDF 9* and Kallsettin (CAG) genes and development symptoms in geniims. According to the results, the PRG gene type of birth weight affected, but did not reduce weight or average daily gains. Interestingly, there was no connection between growing symptoms before lashing and *GDF9*.

Role of *GDF9* and *BMP15* in Reproductive Performance

The *GDF -9* and *BMP -15*, members of the TGF family, are important in many aspects of general follicular development, including OOCT development, granulosa cell function and follicle maturation. Her significant contribution to female reproduction and infertility is widely displayed in scientific studies (37). Both factors are crucial for general reproduction processes and may be fetal development indicators. They regulate the oocyte supply of granulosa cells, form a defense against reactive oxygen species and provide essential nutrients to oocyte through mechanisms such as cholesterol synthesis and glycoliasis (38). The *GDF-9* and *BMP-15* regulate synergistic folkulogenesis and oocyte development. These two proteins are expressed at the same time in oocytes and affect the surrounding granulosa cells. *GDF -9* and *BMP -15* Specific Krein/Treatonin Kinease receptors located on granulosa cells, trigger intracellular signaling cascade.

This activation leads to phosphorus of smading protein, especially SMAD2 and SMAD3, which later produces complexes with SMAD4. These complexes are translated into the core, where they regulate the transcript of the target genes required for granulosa cell proliferation, discrimination and follicle development. CO interaction between *GDF -9* and *BMP -15* improves the efficiency of these processes, facilitating the correct maturity of follicles and ookates (38). Both *GDF-9* and *BMP-15* prevent gonadotropin-retained progesterone excretions. In addition, these two paracrin factor Cumylas, separated by oocytes, spread of cumylus cell, apoptosis, metabolism and expansion (39). Oocyte derivative development factor *GDF-9* and *BMP-15* are expressed selectively by oocytes by oocytes to juggle with the primardia stage and the size of garbage are affected cooperating during public development (40). In addition, *BMP-15* and *GDF-9* control the expression of Hyaluronan Synthse 2, which is necessary for the formation of matrix to accumulate cell expansion, which contributes to the stimulation of cell extension (41).

CONCLUSION

This review concluded that the *GDF9* is essential for folliculogenesis, ozogenesis and ovulation, and therefore female plays an important role in fertility. The *BMP15* Association study was designed to connect *BMP15* -gene polymorphism with physical symptoms in Iraqi roof beard. *BMP15* and *GDF9* promote the development of primary follicles and primary Romans' infections from primidal. They also play an important role in promoting the existence and development of primary follicles in the newborn ovaries. In particular, *GDF9* and *BMP-15* show synergist effects on each other. The breasts should be aware of the importance of *BMP15* and *GDF9* as reproductive indicators, as any disruption in their expression can lead to impaired fertility in animals. Future research should focus on their functional impact on ovulation and development paths to identify specific mutations in *BMP15* and *GDF9* and improve reproductive strategies.

REFERENCES

1) Giannenas, I., Bonos, E., Anestis, V., Filioussis, G., Papanastasiou, D. K., Bartzanas, T.,& Skoufos, I. (2017). Effects of protease addition and replacement of soybean meal by corn gluten meal on the growth of broilers and on the environmental performances of a broiler production system in Greece. *PloS one*, 12(1), e0169511.

2) Wang, J., Liu, Y., Guo, S., Di, R., Wang, X., He, X., & Chu, M. (2024). Polymorphisms of the BMPR1B, BMP15 and GDF9 fecundity genes in four Chinese sheep breeds. *Archives Animal Breeding*, 67(1), 51-60.

3) Pinheiro, J. B., Figueira, L. M., Correia, L. F., Oliveira, T. A., Brair, V. L., Barros, F. F., ... & Souza-Fabjan, J. M. (2023). The coasting time affects the quality of cumulus-oocyte complexes in super stimulated ewes. *Theriogenology*, *196*, 236-243.

4) DENISKOVA, T., SHAKHIN, A., ESMAILIZADEH, A., DOTSEV, A., &

ZINOVIEVA, N. (2023). ANALYSIS OF POLYMORPHISM IN THE MAJOR GENES FOR REPRODUCTIVE TRAITS IN SHEEP (Ovis spp.). *hormones*, *9*, 11.

5) Hartatik, T., Chairunissa, F. A. Z., Bintara, S., Fadillah, F. J., Ningrum, N. P., Puspitasari, D., & Kustantinah. (2023). Mutation analysis and restriction site mapping of GDF9 in Indonesian Bligon goat polymor. *Tropical Animal Science Journal*, 46(2):163-171.

6) Son, Y. L., Ubuka, T., & Tsutsui, K. (2022). Regulation of stress response on the hypothalamic-pituitary-gonadal axis via gonadotropin-inhibitory hormone. *Frontiers in Neuroendocrinology*, *64*, 100953.

7) Muhaghegh Dolatabady, M., & Habibizad, J. (2019). Single nucleotide polymorphisms (SNPs) of GDF9 gene in Bahmaei and Lak Ghashghaei sheep breeds and its association with litter size. *Iranian Journal of Applied Animal Science*, *9*(3), 427-432.

8) Sahib, M. R., Al-Jaryan, I. L., & Al-Thuwaini, T. M. (2024). GDF9 gene c. 260G> A mutation and sheep litter size: a meta-analysis. *Journal of the Hellenic Veterinary Medical Society*, *75*(2), 7493-7500.

9) Turathum, B., Gao, E. M., & Chian, R. C. (2021). The function of cumulus cells in oocyte growth and maturation and in subsequent ovulation and fertilization. *Cells*, *10*(9), 2292.

10) Wang, F., Chu, M., Pan, L., Wang, X., He, X., Zhang, R., ... & Di, R. (2021). Polymorphism detection of GDF9 gene and its association with litter size in Luzhong mutton sheep (Ovis aries). *Animals*, *11*(2), 571.

11) Hossain, M. I., Khan, M. K. I., Momin, M. M., & Das, A. (2020). Effects of protein supplements on fertility and assessment of the fertility genes (GDF9 and BMP15) in indigenous sheep of Bangladesh. *Journal of Applied Animal Research*, *48*(1), 484-491.

12) Kadhem, A. F., & Al-Thuwaini, T. M. (2022). Influence of litter size on the hematologic profile of Awassi ewes during gestation and lactation. *Vet Integr Sci* 20(3): 625-633. https://doi. org/10.12982/VIS. 2022.047

13) Patiño, L. C., Walton, K. L., Mueller, T. D., Johnson, K. E., Stocker, W., Richani, D., ... & Harrison, C. A. (2017). BMP15 mutations associated with primary ovarian insufficiency reduce expression, activity, or synergy with GDF9. *The Journal of Clinical Endocrinology & Metabolism*, *102*(3), 1009-1019.

14) Pinheiro, J. B., Figueira, L. M., Correia, L. F., Oliveira, T. A., Brair, V. L., Barros, F. F., ... & Souza-Fabjan, J. M. (2023). The coasting time affects the quality of cumulus-oocyte complexes in super stimulated ewes. *Theriogenology*, *196*, 236-243.

15) Wang, W., Rigueur, D., & Lyons, K. M. (2020). TGFβ as a gatekeeper of BMP action in the developing growth plate. *Bone*, *137*, 115439.

16) Drobik-Czwarno, W., Martyniuk, E., Nowak-Życzyńska, Z., Kaczor, U., & Kucharski, M. (2021). Frequency of BMP15 and GDF9 mutations increasing litter size and their phenotypic effects in Olkuska sheep population. *Annals of Animal Science*, *21*(1), 89-108.

17) Di, R., Wang, F., Yu, P., Wang, X., He, X., Mwacharo, J. M., ... & Chu, M. (2021). Detection of novel variations related to litter size in BMP15 gene of luzhong mutton sheep (Ovis aries). *Animals*, *11*(12), 3528.

18) Chen, Y., Shan, X., Jiang, H., Sun, L., & Guo, Z. (2023). Regulation of litter size in sheep (Ovis aries) by the GDF9 and BMP15 genes. *Annals of Agricultural Sciences*, *68*(2), 148-158.

19) Albarella, S., Ciotola, F., Selvaggi, M., Dario, C., Licciardi, S., Scopino, G., ... & Peretti, V. (2015). Analysis of major fecundity genes in autochthonous Laticauda and Bagnolese sheep breeds. *Small Ruminant Research*, *133*, 118-122.

20) Wang, F., Chu, M., Pan, L., Wang, X., He, X., Zhang, R., ... & Di, R. (2021). Polymorphism detection of GDF9 gene and its association with litter size in Luzhong mutton sheep (Ovis aries). *Animals*, *11*(2), 571.

21) Marzanov, N. S., Devrishov, D. A., Ozerov, M. Y., Maluchenko, O. P., Marzanova, S. N., Shukurova, E. B., ... & Petit, D. (2023). The significance of a multilocus analysis for assessing the biodiversity of the Romanov sheep breed in a comparative aspect. *Animals*, *13*(8), 1320.

22) Lassoued, N., Benkhlil, Z., Woloszyn, F., Rejeb, A., Aouina, M., Rekik, M., ... & Bedhiaf-Romdhani, S. (2017). FecX Bar a Novel BMP15 mutation responsible for prolificacy and female sterility in Tunisian Barbarine Sheep. *BMC genetics*, *18*, 1-10.

23) Sarma, L., Nahardeka, N., Zaman, G., Aziz, A., Das, A., Akhtar, F., ... & Borkolita, L. (2019). Analysis of BMP4 gene HaeIII polymorphism in Assam Hill goat. *J Entomol Zool Stud*, *7*(2), 34-37.

24) Kumar, S., Rajput, P. K., Bahire, S. V., Jyotsana, B., Kumar, V., & Kumar, D. (2020). Differential expression of BMP/SMAD signaling and ovarian-associated genes in the granulosa cells of FecB introgressed GMM sheep. *Systems biology in reproductive medicine*, *66*(3), 185-201.

25) Ali, M. A., Kadhim, A. H., & Al-Thuwaini, T. M. (2022). Genetic variants of the bone morphogenetic protein gene and its association with estrogen and progesterone levels with litter size in Awassi ewes. *Iraqi J Vet Sci* 36(4):1017–1022.

26) Imran, F. S., & Al-Thuwaini, T. M. (2024). The novel C268A variant of BMP2 is linked to the reproductive performance of Awassi and Hamdani sheep. *Molecular Biology Reports*, *51*(1), 267.

27) Magro-Lopez, E., & Muñoz-Fernández, M. Á. (2021). The role of BMP signaling in female reproductive system development and function. *International journal of molecular sciences*, *22*(21), 11927.

28) Tian, Y. Q., Li, X. L., Wang, W. J., Hao, H. S., Zou, H. Y., Pang, Y. W., Zhao, X. M., Zhu, H. B., & Du, W. H. (2022). Knockdown of bone morphogenetic protein 4 gene induces apoptosis and inhibits proliferation of bovine cumulus cells. *Theriogenology*,188,28–36.

29) L Sarma, N Nahardeka, G Zaman, A Aziz, A Das, F Akhtar, S Upadhyay and L Borkolita.(2019). Analysis of BMP4 gene HaeIII polymorphism in Assam Hill goat. *JEZS* ; 7(2): 34-37

30) Tang, J., Hu, W., Di, R., Liu, Q., Wang, X., Zhang, X., ... & Chu, M. (2018). Expression analysis of the prolific candidate genes, BMPR1B, BMP15, and GDF9 in Small Tail Han ewes with three fecundity (FecB gene) genotypes. *Animals*, *8*(10), 166.

31) Pan, Z. Y., Di, R., Tang, Q. Q., Jin, H. H., Chu, M. X., Huang, D. W., ... & Song, C. L. (2015). Tissue-specific mRNA expression profiles of GDF9, BMP15, and BMPR1B genes in prolific and non-prolific goat breeds. *Anim. Sci.60:452–458.*

32) Getmantseva, L., Bakoev, N., Shirokova, N., Kolosova, M., Bakoev, S., Kolosov, A., ... & Yuri, K. (2019). Effect of the GDF9 gene on the weight of lambs at birth. *Bulg J Agric Sci*. 25(1):153–157.

33) Torres, T. S., Sena, L. S., Ó, A. O. D., Santos, G. V. D., Rocha, A. O., & Sarmento, J. L. R. (2021). Influence of non-genetic factors on the maternal ability of Santa Inês ewes. *Ciência Rural*, *51*(6), e20200580.

34) Selionova, M. I., & Podkorytov, N. A. (2021). Polymorphism of the gene GDF9 in sheep of Prikatun type of Altai Mountains breedand its correlation with indices of meat rate productivity. *Теория и практика переработки мяса*, *6*(1), 4-9.

35) Al-Khuzai, F. L. J., & Ahmed, J. R. (2019). Polymorphism of GDF9 (exon-1) gene and its association with milk production and prolificacy of Awassi sheep. *Genet Eng Biotechnol.* 19(1):85–95.

36) Jawasreh, K. I., & Ismail, Z. B. (2018). Polymorphism of prolactin, growth differentiation factor 9, and calpastatin genes and their effects on weight traits in Awassi lambs. *Journal of Advanced Veterinary and Animal Research*, *6*(1), 86.

37) Riepsamen, A. H., Donoghoe, M. W., Indran, I. R., Hechtman, L., Robertson, D. M., Gilchrist, R. B., ... & Yong, E. L. (2023). Serum GDF9 and BMP15 as potential markers of ovarian function in women with and without polycystic ovary syndrome. *Clinical Endocrinology*, *98*(4), 567-577.

38) Hassan, M. F., & Abdulhameed, W. A. (2024). Serum Follicular Fluid Growth Differentiation Factor 9 (GDF-9) and Bone Morphogenic Protein 15 (BMP-15) as Markers of Ovarian Reserve. *Al-Anbar Medical Journal*, *20*(1).

39) Heath, D. A., Pitman, J. L., & McNatty, K. P. (2017). Molecular forms of ruminant BMP15 and GDF9 and putative interactions with receptors. *Reproduction*, *154*(4), 521-534.

40) Yu, Y. X., Pan, W. C., & Cheng, Y. F. (2017). Silencing of advanced glycosylation and glycosylation and product-specific receptor (RAGE) inhibits the metastasis and growth of non-small cell lung cancer. *American journal of translational research*, *9*(6), 2760.

41) Cook-Andersen, H., Curnow, K. J., Su, H. I., Chang, R. J., & Shimasaki, S. (2016). Growth and differentiation factor 9 promotes oocyte growth at the primary but not the early secondary stage in three-dimensional follicle culture. *Journal of*

assisted reproduction and genetics, *33*, 1067-1077.