JIVS JOURNAL OF ISTANBUL VETERINARY SCIENCES

The effects of KISS1, GDF9 and BMP15 genes on reproductive traits in goats: A review

Berk Özcan ATALAY[1], Atila ATEŞ[2]

1.Istanbul University-Cerrahpasa, Institute of Graduate Studies, Department of Veterinary Biochemistry. Istanbul, Turkey. 2. Istanbul University-Cerrahpasa, Faculty of Veterinary Medicine, Department of Biochemistry. Istanbul, Turkey.

Atalay, B. Ö. ORCID: 0000-0002-1749-0638; Ates, A. ORCID: 0000-0002-9013-930X

Review Article
Volume: 8, Issue: 2
August, 2024
Pages: 172-177

Article History
Received: 05.05.2024
Accepted: 25.07.2024
Available online: 30.07.2024

ABSTRACT

This review article presents a comprehensive analysis of the genetic factors determining reproductive performance in goats. Reproductive capacity is a critical parameter that directly affects economic efficiency in the livestock industry. Genetic studies have enabled the identification of various genes and genetic mechanisms influencing reproductive performance in goats, including key genes such as KISS1, GDF9 and BMP15. It is essential to examine the reproductive conditions and traits in farm animals, particularly in indigenous goat breeds historically, culturally, and economically significant in our country. This review examines KISS1, GDF9 and BMP15 genes associated with reproduction, their functions, and their impacts on reproductive biology in light of current literature. The importance of modern genetic techniques and biotechnological applications in enhancing reproductive efficiency in goat populations is also discussed. This review provides data for the optimization of gene selection strategies and the integration of current genetic knowledge to improve reproductive performance in goat breeding.

Keywords: goat reproduction, reproductive performance, KiSS1, GDF9, BMP15

DOI: https://doi.org/10.30704/http-www-jivs-net.1489927

To cite this article: Atalay, B. Ö., Ateş, A. (2024). The effects of KISS1, GDF9 and BMP15 genes on reproductive traits in goats: A review. ***Journal of Istanbul Veterinary Sciences, 8*(2), 172-177.** **Abbreviated Title*: J. İstanbul vet. sci.***

Introduction

After dogs, goats (*Capra hircus*), as the second domesticated animal, have provided significant benefits to human agricultural communities by facilitating the transition to settled life through the production of products such as meat, milk, and wool (Porter, 1996; Pringle, 1998; Zeder and Hesse, 2000). Goats are found on every continent except Antarctica, and surprisingly, 93.4% of these animals are located in Asia and Africa. Their presence is crucial in various roles, from livelihood sustenance to agricultural production, spanning from sparsely populated and non-industrialized countries to industrialized ones. Africa raises approximately 35.7% of the world's goat population, with 60% of these animals concentrated in the sub-Saharan region, including countries such as Chad and Ethiopia. (World Population Review, 2021). According to statistics, hair goats make up the largest proportion of the total goat population in Türkiye, accounting for approximately 93% of the total goat herd (Daşkıran et al., 2018). When goat farming is mentioned in Turkey, Hair goats generally come to mind. According to the 2020 Turkish Statistical Institute (TÜİK) data, the goat population is 12,350,811 heads. Hair goats and their crosses account for

---

***Corresponding Author:** Berk Özcan Atalay
berkozcanatalay@gmail.com

approximately 98% of the total goat population, and Angora goats account for 2%. The share of the goat population in our country's small ruminant population is approximately 22.43% (Turkish Statistical Institute, 2024). The suitability of Turkey's natural resources, mainly pastures, for breeding sheep and goat species, as well as factors such as consumption habits in rural areas, create a favorable environment for small ruminant breeding (Kaymakçı et al., 2006).

Primates and many ruminants typically release a single oocyte at each cycle whereas species such as mice and pigs have consistently high ovulation rates. In mammals the ovulation rate and the litter sizes are a result of well-regulated interactions of endocrine and paracrine mediators. How precisely the litter size is controlled remains a critical and essential question in reproductive biology (Polley et al., 2009).

Through genome scans, many genomic regions (Quantitative Trait Loci, QTL) that influence various productive traits have been identified, and candidate gene studies are being conducted to identify genes involved in the physiological regulation of nutrition, growth, and energy metabolism (Schrooten et al., 1996; Ashwell et al., 2004; Weikard et al., 2004). The basis of QTL mapping studies is to determine the relationship between specific genetic markers and phenotypes. In farm animals, marker-QTL linkage studies are generally conducted within populations and require the presence of polymorphic marker regions (Primrose et al., 2006; Weller 2009). Molecular markers in farm animals are extensively used to reveal genetic variation at the DNA level, associate gene regions with economically important traits, or identify single genes affecting a particular trait (Balcıoğlu et al., 2014). The data acquired herein is employed in selection investigations aimed at augmenting productivity within the domain of animal husbandry. The amelioration of reproductive attributes in livestock species has garnered escalating attention, notably in ovine and caprine species, where even marginal enhancements in litter size can yield substantial profitability increments.

Consequently, several studies have been conducted to identify genes and candidate genes associated with fertility traits in goats (Getaneh and Alemayehu, 2022).

In recent years, there has been significant progress in understanding the genetic factors that influence reproductive performance in goats. Among these factors, candidate genes such as KISS1 (Kisspeptin), GDF9 (Growth differentiation factor 9) and BMP15 (Bone morphogenetic protein 15) have garnered considerable attention due to their critical roles in regulating reproductive traits. This review examines these key genes in detail, exploring their functions, the mechanisms by which they impact reproductive biology, and their potential applications in genetic selection strategies. By integrating the latest findings from the current literature, this review will provide a comprehensive overview of how KISS1, GDF9 and BMP15 contribute to enhancing reproductive efficiency in goat populations.

Kisspeptin (KISS1)

The kisspeptin/GPR54 pathway is recognized as a key regulator of pubertal development and reproductive function. Several studies have been conducted on the KISS1 gene as a candidate gene for animal reproductive traits (West et al., 1998). KISS1 neurons in the hypothalamus contribute to crucial aspects of reproductive maturation and function, such as sexual differentiation at the brain level, the onset of puberty, and the neuroendocrine regulation of gonadotropin secretion and ovulation (Caraty et al., 2010). So far, the literature on KISS1 and goat reproduction is limited. Due to the importance of KISS1 as a regulator of puberty onset, it is likely that polymorphisms in this gene may be associated with some reproductive traits in goats, such as high productivity, precocious puberty, and year-round estrus phenotypes (Sharma et al., 2013).

According to genetic research, the KISS1 gene is a major fecundity gene in goats. Polymorphisms of the KISS1 gene were associated with higher litter size (Cao et al., 2010; An et al., 2013).

The KISS1 gene in goats is located in chromosome 16. KISS1 gene consists of two coding regions (exons) and one single non-coding region (intron), and the transcript length is 408 bp and encodes 135 amino acids. This gene reaches around 2.62 kilobases (Febriana et al., 2022). This gene encodes a family of neuropeptides called kisspeptins, which activate G protein-coupled receptor-54 (GPR54) (Ohtaki et al., 2001; Yeo and Colledge, 2018; Harter et al., 2018).

In a study conducted on 90 female goats, consisting of 30 individuals from each of the Kacang, Kejobong, and Senduro breeds, the sequence alignment analysis revealed one insertion/deletion and fourteen polymorphic sites in the intron 1 KISS1 gene on three Indonesian native goat breeds. SNP9 at intron 1 of the KISS1 gene was found to be in strong linkage with SNP8 and SNP10; and identified to have a significant association with litter size and parity. Furthermore, the does with H2 haplotype (CCATAGCGCAACGT) had higher litter size than those other haplotypes (Febriana et al., 2022).

In another study conducted using the PCR-RFLP method on 124 animals, comprising 62 Cyprus goats and 62 Iraqi black goats, three polymorphic sites (with transversion mutations) in exon 1 (893G>C, 973C>A, and 979T>G) were detected. The reference sequences of the gene (ID: JX047312.1 for Cyprus goat samples and KC989928.1 for Iraqi black goat samples) were used for comparison. The results of this study showed that polymorphisms of the KiSS1 gene cause an increase of the litter size in two goat breeds. The genetic diversity of polymorphism content in combination with genotypes of different KiSS1 gene loci was associated with litter size performed in both Cyprus and Iraqi black Doe at locus g. 893G>C. Significant ($P<0.05$) genetic diversity was determined at that locus in the HWE test in Cyprus and Iraqi black goats (Rahawy and Al-Mutar, 2021).

In a study that utilized 723 goats belonging to three breeds, including 306 Xinong Saanen, 221 Guanzhong, and 196 Boer, the SNPs of the KISS1 gene were genotyped by PCR-RFLP. Two SNPs (g.2124T>A and g.2270C>T) were genotyped in the three goat breeds. These two SNP loci were in Hardy-Weinberg disequilibrium in the SN and GZ breeds ($P < 0.05$), which showed that the genotypic frequencies had been affected by selection, mutation or migration (An et al., 2013).

In another study conducted on 89 Gaddi goats, the PCR-RFLP assay revealed polymorphism in the amplified product of intron 1 of the kisspeptin (KISS1) gene in the migratory Gaddi goat population. DNA sequencing confirmed one nucleotide mutation (T125A) in the intron 1 region of the KISS1 gene with the allelic frequency of alleles A and B as 0.43 and 0.57, respectively. A significant association with T allele for litter size was observed in screened migratory Gaddi goats (Sankhyan et al., 2020).

Growth differentiation factor 9 (GDF9)

The growth differentiation factor 9 (GDF9) gene is one of the most important fecundity genes that widely studied in goats belonging to the transforming growth factor β (TGFβ) superfamily. The protein is one of the important fecundity genes which plays a critical role during early folliculogenesis as a growth and differentiation factor secreted by oocytes in mammals (Elvin et al,. 1999).

Mammalian oocytes secrete GDF9 and is a key regulator of follicular proliferation, ovulation and fertilization, and also improves the developmental competence of oocytes in females (Wang et al., 2019). The secretion of GnRH stimulates the release of gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary gland, ultimately controlling gonadal function (Jih and Wu, 1995; Fulghesu et al., 1997).

The GDF9 gene is located on caprine Chromosome 7 and has a coding region of 4720 base pairs and two exons. Many single nucleotide polymorphisms (SNPs) that have been identified in the gene, and the SNPs have been reported influence on litter size in goats. The most common SNP in the caprine GDF9 gene is V397I or c.1198G>A located on exon (Mahmoudi et al., 2019).

Literature has shown that the V397I SNP was polymorphic in many goat populations while non-polymorphic in other goat breeds (Polley et al., 2009). A study investigated the polymorphisms of GDF9 genes in 641 goats of three breeds: Xinong Saanen, Guanzhong and Boer. The biochemical and physiological functions, together with the results obtained in the investigation, suggest that the GDF9 genes could serve as genetic markers for litter size in goat breeding (An et al., 2012).

Feng et al (2011) concluded that the C allele at locus 959 of the GDF9 gene was associated with high litter size in Jining Grey goats ($P < 0.01$).

In a study, 48 female Pote goats from smallholder farms were utilised, with a range of permanent incisive (0, 1, 2, 3, 4). A survey method was used to collect data on the litter size of Pote goats and the PCR-RFLP method was used for laboratory observation to detect GDF9 gene polymorphism. This study shows that GDF9 gene polymorphism is associated with litter size of Pote goats. Based on these results, it means that the GDF9 gene mutation is significantly associated with the litter size trait in Pote goats, and the genetic variant of the GDF9 gene is considered as a genetic marker for increased proliferation in Pote goats (Imaniah et al., 2023).

In another study, the investigation was conducted to identify point mutations in two goat breeds from Indonesia, namely Kosta and Lakor, native livestock from Banten and Southwest Maluku regency, respectively. This investigation specifically targeted the analysis of exon region 1 of the GDF9 about litter size ability in both breeds. The multiple alignment results of exon-1 from the GDF9 gene revealed the presence of 2 nucleotides with mutations. However, it was observed that these mutations did not result in the encoding of different amino acids. This suggests that the mutation is associated with the litter size of Lakor and Kosta goat populations (Rumanta et al., 2023).

In a study conducted on 15 local Iraqi Bucks, direct sequencing was used to screen potential SNP loci in the goat GDF9 exon one. As a result, one SNP locus site, 2006 CTC < CTA (leu < leu), was positively identified. This study is the first to show a significant association of GDF9 in the initiation or maintenance of spermatogenesis in male goats (Jassim and Al-Azzawi, 2022).

In another large-scale study, 45 SNP loci were gathered and sorted from the goat GDF9 gene. The main focus of the analysis and discussion revolved around the relationship between a subset of potentially "true" SNPs and the reproductive traits of goats. Among these mutations, three non-synonymous mutations A240V, Q320P, and V397I and three synonymous mutations L61L, N121N, and L141L were found to have a high mutant frequency in many fecundity goat breeds. Particularly, the mutations Q320P, V397I, L61L, and N121N exhibited high frequencies, ranging from 0.5 to 0.7. According to the summary and analytic results of the current SNP loci within the goat GDF9 gene in this study, it was found that A240V, Q320P, V397I, L61L, N121N, and L141L are six effective SNPs associated with the litter size trait. In most goat breeds worldwide, the V397I and L61L mutations showed a negative relationship with strong goat fertility, and the other four SNPs exhibited a positive effect (Wang et al., 2019).

Bone morphogenetic protein 15 (BMP15)

The critical role of BMP15 in early follicle growth is species-specific and revealed to be related to mono-polyovulatory animals (Moore and Shimasaki, 2005).

BMP15 regulates granulosa cell proliferation and differentiation by promoting granulosa cell mitosis, suppressing follicle-stimulating hormone receptor expression, and stimulating kit ligand expression. These functions play a pivotal roles in female fertility in mammals (Juengel et al., 2002).

There is a high influence of BMP15 and GDF9 on fecundity. These genes are produced by the ovary and influence its function. In addition to increasing the ovulation rate in goats, they also affect follicle growth and development at all stages of follicular genesis in females (Getaneh and Alemayehu, 2022).

Bone morphogenetic protein 15 (BMP15) is a member of the TGFβsuperfamily that is especially expressed in oocytes. The goat BMP15 gene maps to the X chromosome (Farhadi et al., 2013).

In a study of the association of the bone morphogenetic protein 15 (BMP15) gene with the prolific characteristics of Surti goats managed under farm and field conditions, it is claimed that a mutation in the Exon-2 region of the BMP15 gene, with a base size of 575 bp, increases litter size. In total, 100 Surti goats were involved in the study, revealing the presence of two polymorphic sites. One site was identified at 500 base pairs, while the other was found at 400 base pairs. Out of the 100 Surti goats examined, 58 were identified with the AA genotype, while 29 had the AB genotype, and 13 had the AC genotype. A polymorphic region at 500 bp (AB genotype) plays a highly significant role in the higher prolificacy of Surti goats as compared to base size 575 bp (AA genotype) and polymorphic site 400 bp (AC genotype). Polymorphic region AB may be used as a marker genotype for early age selection of female Surti goat. It is claimed that the polymorphic region AB may be used as a marker genotype for early age selection of female Surti goats (Dangar et al., 2022).

In addition, the association of BMP15 gene with prolificacy/litter size was investigated in Jamunapari and crossbred goats (Shaha et al., 2022), in Haimen, Boer, and Huanghui goat breeds of China (He et al., 2010), and Markhoz goats of Iran (Ghoreishi et al., 2019; Getaneh and Alemayehu, 2022).

Polymorphisms of BMP15 gene exon 2 and its relationship with the prolificacy of goats were detected by PCR-SSCP and DNA sequencing methods in two Chinese local goat breeds (Wang et al., 2011).

In a study, 200 adult female Markhoz goats were examined with the PCR-RFLP method for the FecXH, FecXI, FecXG and FecXB mutations. The results showed no polymorphism in the tested Markhoz goats (Shokrollahi, 2015). However, in another study, the mutation of BMP15 genes associated with the goat fecundity has been confirmed in Markhoz goats (Paulini and de Oliveira Melo 2011).

In contrast, homozygous mutant animals showed higher numbers of kids in Beetal goats (Islam et al., 2019).

Conclusion

This review underscores the critical roles of the KISS1, GDF9, and BMP15 genes in managing reproductive traits in goats. Each of these genes uniquely contributes to reproductive efficiency, affecting crucial aspects such as the onset of puberty, follicle development, ovulation, and litter size.

The KISS1 gene is essential for starting puberty and regulating reproductive functions through the neuroendocrine system. Variations in this gene are linked to better reproductive outcomes, including larger litter sizes. The GDF9 gene is vital for early follicle development, with several variations associated with increased fertility, making it a valuable marker for breeding programs. The BMP15 gene also plays a key role in the growth and differentiation of granulosa cells, with its variations linked to higher fertility in different goat breeds.

Incorporating genetic knowledge about KISS1, GDF9, and BMP15 into breeding strategies offers significant potential for improving goat reproductive performance. Advances in genetic technologies and biotechnological applications allow for precise selection and breeding decisions, boosting productivity and economic efficiency in the livestock sector. This review highlights the need for ongoing research into these genes to develop optimized genetic selection strategies, enhancing goat breeding programs by leveraging current genetic insights.

References

An, X. P., Hou, J. X., Zhao, H. B., Li, G., Bai, L., Peng, J. Y., Yan, Q. M., Song, Y. X., Wang, J. G., & Cao, B. Y. (2012). Polymorphism identification in goat GnRH1 and GDF9 genes and their association analysis with litter size. *Animal Genetics, 44*, 234-238.

An, X., Ma, T., Hou, J., Fang, F., Han, P., Yan, Y., Zhao, H., Song, Y., Wang, J., & Cao, B. (2013). Association analysis between variants in KISS1 gene and litter size in goats. *BMC Genetics, 14*(63), 1-6.

An, X., Han, P., Hou, J., Zhao, H. B., Yan, Y., Ma, T., Fang, F., Meng, F., Song, Y. X., Wang, J. G., & Cao, B. (2013). Molecular cloning and characterization of KISS1 promoter and effect of KISS1 gene mutations on litter size in the goat. *Genetics and Molecular Research: GMR, 12(*4), 4308-4316.

Ashwell, M. S., Hayen, D. W., Sonstegard, T. S., Van Tanssell, C. P., Da, Y., VanRaden, P. M., Ron, M., Weller, J. I. & Lewin, H. A. (2004). Detection of quantitative trait loci affecting milk production, health and reproductive traits in Holstein cattle. *Journal of Dairy Science, 87*, 468-475.

Balcıoğlu, M. S., Karslı, T., Şahin, E., Ulutaş, Z. & Aksoy, Y. (2014). Türkiye'de yetiştirilen bazı yerli koyun ırklarında kalpastatin (CAST) geni polimorfizminin PCR-RFLP yöntemiyle belirlenmesi. *Journal of Agricultural Sciences, 20*, 427-433.

Caraty, A., Franceschini, I., & Hoffman, G. E. (2010). Kisspeptin and the preovulatory gonadotrophin-releasing hormone/luteinising hormone surge in the ewe, basic aspects and potential applications in the control of ovulation. *Journal of Neuroendocrinol, 22*, 710–715.

Cao, G., Chu, M., Fang, L. J., Di, R., Feng, T., & Li, N. (2010). Analysis on DNA sequence of KiSS-1 gene and its association with litter size in goats. *Molecular Biology Reports, 37*, 3921-3929.

Dangar, N. S., Pandya, G. M., Ramani, U. V., Kharadi, V. B., & Brahmkshtri, B. P. (2022). Association study of fecundity gene BMP 15 with prolificacy in surti goats under farm and field condition of South Gujarat Region. *Indian Journal of Veterinary Sciencesand Biotechnology, 18,* 100-104.

Daşkıran, İ., Savaş, T., Koyuncu, M., Koluman, N., Keskin, M., Esenbuğa, N., Konyalı, A., Cemal, İ., Gül, S., Elmaz, Ö., Koşum, N., Dellal, G., & Bİngöl, M. (2018). Goat production systems of Turkey: Nomadic to industrial. *Small Ruminant Research, 163*, 15-20.

Elvin, J. A., Clark, A. T., Wang, P., Wolfman, N. M., & Matzuk, M. M. (1999). Paracrine actions of growth differentiation factor-9 in the mammalian ovary. *Molecular Endocrinology, 13*(6), 1035-1048.

Farhadi, A., Genualdo, V., Perucatti, A., Hafezian, S.H., Rahimi -Mianji, G., De Lorenzi, L., Parma, P., Iannuzzi, L., & Iannuzzi, A. (2013). Comparative FISH mapping of BMPR1B, BMP15 and GDF9 fecundity genes on cattle, river buffalo, sheep and goat chromosomes. *Journal of Genetics, 92*(3), 595-597.

Febriana, A., Sutopo, S., Kurnianto, E., & Widiyanto, W. (2022). A Novel SNPs of KISS1 gene strongly associated with litter size in indonesian goat breeds. *Tropical Animal Science Journal*. 45(3), 255-269.

Feng, T., Geng, C. X., Lang, X. Z., Chu, M. X., Cao, G. L., Di, R., Fang, L., Chen, H. Q., Liu, X. L., & Li, N. (2011). Polymorphisms of caprine GDF9 gene and their association with litter size in Jining Grey goats. *Molecular Biology Reports, 38*, 5189-5197.

Fulghesu, A. M., Lanzone, A., Apa, R., Guido, M., Ciampelli, M., Cucinelli, F., Caruso, A., & Mancuso, S. (1997). The hypothalamic-pituitary-luteal axis in women: effects of long-term orally active opioid antagonist (naltrexone) administration. *Journal of Endocrinological Investigation, 20*, 368-373.

Getaneh, M., & Alemayehu, K. (2022). Candidate genes associated with economically important traits in dairy goats. *Cogent Food & Agriculture, 8*(1), 2149131, 1-39.

Ghoreishi, H., Fathi-Yosefabad, S., Shayegh, J., & Barzegari, A. (2019). Identification of mutations in BMP15 and GDF9 genes associated with prolificacy of Markhoz goats. *Archives Animal Breeding, 62*(2), 565-570.

Harter, C. J., Kavanagh, G. S., & Smith, J. (2018). The role of kisspeptin neurons in reproduction and metabolism. The *Journal of endocrinology, 238,* 3, R173-R183.

He, Y., Ma, X., Liu, X., Zhang, C., & Li, J. (2010). Candidate genes polymorphism and its association to prolificacy in Chinese goats. *Journal of Agricultural Science, 2*(1), 88-92.

Imaniah, N. H., Susilorini, T. E., Kuswati, K., & Wahyuni, R. D. (2023). GDF9 gene polymorphism and its relation to litter size in East Java Pote goat germplasm. *BIO Web of Conferences, The 4th International Conference on Environmentally Sustainable Animal Industry (ICESAI 2023),* 81, 7. https://doi.org/10.1051/bioconf/20238100007

Islam, M., Basheer, A., Javed, K., Anjum, A., & Zahoor, I. (2019). PCR-RFLP-based identification of polymorphisms in BMPR1B, GDF9, and BMP15 genes associated with litter size in Beetal and Teddy goats. South *African Journal of Animal Science, 49*, 697.

Jassim, A., & Al-Azzawi, S. H. (2022). Estimation of genetic variance based on the growth differentiation factor 9 (GDF9) gene and its association with semen quality in local Iraqi goats. *Diyala Agricultural Sciences Journal*, 14, 14-20.

Jih, M. H., & Wu, T. C. J. (1995). Altered regulation of pituitary luteinizing hormone secretion by GnRH and inhibin in the aged persistent-estrous female rat. *Mechanisms of Ageing and Development, 84*, 15–27.

Juengel, J. L., Hudson, N. L., Heath, D. A., Smith, P., Reader, K. L., Lawrence, S. B., O'Connell, A. R., Laitinen, M. P., Cranfield, M., Groome, N. P., Ritvos, O., & McNatty, K. P. (2002). Growth differentiation factor 9 and bone morphogenetic protein 15 are essential for ovarian follicular developmentin sheep. *Biology of Reproduction, 67*(6), 1777-1789.

Kaymakçı, M. (2006). Keçi Yetiştiriciliği. *İzmir ili damızlık koyun-keçi yetiştiricileri birliği yayınları, No:2*. Bornova-İzmir, Türkiye.

Kaymakçı, M., Koşum, N., Taşkın, T. & Akbaş, Y. (2006). Menemen koyunlarında kimi verim özelliklerinin belirlenmesi üzerine bir araştırma. *Ege Üniversitesi Ziraat Fakültesi Dergisi 43*, 63-74.

Mahmoudi, P., Rashidi, A., Rostamzadeh, J., & Razmkabir, M. (2019). Association between c.1189G>A. *Reproduction Science, 209*, 106140.

Moore, R.K., & Shimasaki, S. (2005). Molecular biology and physiological role of the oocyte factor, BMP-15. *Molecular Cell Endocrinology, 234*(1-2), 67-73.

Ohtaki, T., Shintani, Y., Honda, S., Matsumoto, H., Hori, A., Kanehashi, K., Terao, Y., Kumano, S., Takatsu, Y., Masuda, Y., Ishibashi, Y., Watanabe, T., Asada, M., Yamada, T., Suenaga, M., Kitada, C., Usuki, S., Kurokawa, T., Onda, H., Nishimura, O., & Fujino, M. (2001). Metastasis suppressor gene KiSS-1 encodes peptide ligand of a G-protein-coupled receptor. *Nature, 411*, 613-617.

Paulini, F., & de Oliveira Melo, E. (2011). The role of oocyte-secreted factors GDF9 and BMP15 in follicular development and oogenesis. *Reproduction in domestic animals = Zuchthygiene, 46*(2), 354-361.

Primrose, S. B. & Twyman, R. M. (2006). Principles of gene manipulation and genomics. 7th edition. Malden-Blackwell, United States of America.

Pringle, H. (1998). Neolithic agriculture:reading the signs of ancient animal domestication. *Sciences, 282*, 1448.

Polley, S., De, S., Batabyal, S., Kaushik, R., Yadav, P., Arora, J. S., et al. (2009). Polymorphism of fecundity genes (BMPR1B, BMP15 and GDF9) in the Indian prolific Black Bengal goat. *Small Ruminant Research, 85*(2-3), 122-129.

Porter, V. (1996). Goats of the world. Farming pres. Ipswich, United Kingdom.

Rahawy, M. A., & Al-Mutar, H. A. (2021). Association of the KiSS1 gene with litter size in Cyprus and Iraqi black goats. *Veterinary World, 14*, 1995-2001.

Rumanta, M., Kunda, R. M., Volkandari, S. D., & Munir, I. M., (2023). Impact of Environmental Geographic toward Point Mutations in Exon 1 of Growth Differentiation Factor (GDF9) Gene in Kosta and Lakor Goat Breeds. *Jurnal Penelitian Pendidikan IPA, 9*(6), 4813-4819

Sankhyan, V., Thakur, Y. P., & Dogra, P. K. (2020). Association of kisspeptin gene (KISS1) with litter size in migratory Gaddi goats in western Himalayan state of Himachal Pradesh. *The Indian Journal of Animal Sciences. 89*(12), 1352-1355.

Schrooten, C., Bovenhuis, H., Coppieters, W., & Van Arendonk, J. A. M. (1999). Whole genome scan to detect quantitative trait loci for conformation and functional traits in dairy cattle. *Journal of Dairy Science. 83*, 795-806.

Shaha, M., Miah, G., Lima, A., Miazi, O. F., Gupta, M. D., & Das, A. (2022). Identification of polymorphisms in GDF9 and BMP15 genes in Jamunapari and crossbred goats in Bangladesh. *Tropical Animal Health and Production, 54*(6), 350.

Sharma, A., Dutt, G., Jayakumar, S., Saroha, V., & Verma, N. K., 2013. Genetic structuring of nine Indian domestic goat breeds based on SNPs identified in IGF-1 gene. *Animal Biotechnology, 24*, 148-157.

Shokrollahi, B. (2015). Investigation of BMP15 gene polymorphisms associated with twining in Markhoz goat. *Biharean Biologist, 9*, 1-4.

Turkish Statistical Institute. (2024). Homepage. Turkish Statistical Institute. Retrieved May 2024, from http://www.tuik.gov.tr/Start.do

Wang, X., Yang, Q., Wang, K., Yan, H., Pan, C., Chen, H., et al. (2019). Two strongly linked single nucleotide polymorphisms (Q320P and V397I) in GDF9 gene are associated with litter size in cashmere goats. *Theriogenology, 125*, 115–121.

Wang, X., Yang, Q., Zhang, S., Zhang, X., Pan, C., Chen, H., Zhu, H., & Lan, X. (2019). Genetic effects of single nucleotide polymorphisms in the goat GDF9 gene on prolificacy: True or false positive? *Animals (Basel), 9*(11), 886.

Wang, Y.Q., Li, Y.X., Zhang, N., Wang, Z.B., & Bai, J.Y. (2011). Polymorphism of exon 2 of BMP15 gene and its relationship with litter size of two Chinese goats. *Asian-Australasian Journal of Animal Sciences, 24*(7), 905-911.

Weikard, R., Kühn, C., Goldammer, T., Freyer, G. & Schwerin, M. (2004). The bovine PPARGC1A gene: molecular charaterization and association of an SNP with variation of milk fat synthesis. *Physiological Genomics. 21*, 1-13.

Weller, J. I. (2009). *Quantitative trait loci analysis in animals. Modular Texts.* Cambridge, United States of America.

West, A., Vojta, P. J., Welch, D. R., & Weissman, B. E. (1998). Chromosome localization and genomic structure of the KiSS1 metastasis suppressor gene (KiSS1). *Genomics, 54*, 145-148.

World Population Review. (2021). Goat Population by Country. World Population. Retrieved May 2024 from https://worldpopulationreview.com/country-rankings/goat-population-by-country

Yeo, S. & College, W. H. (2018). The role of KiSS 1 neurons as integrators of endocrine, metabolic, and environmental factors in the hypothalamic–pituitary–gonadal axis. *Frontiers in Endocrinology, 9*(188), 1-13.

Zeder, M. A., & Hesse, B. (2000). The initial domestication of goats (Capra hircus) in the Zagros Mountain 10000 years ago. *Science. 287*, 2254-2257.