



Review Article

Cytochrome-P450 (*CYP11B1* Gene) Polymorphism and its Role in Bovine Milk Producing Traits

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Abstract | A newly developed strategy with enormous promise is genomic selection for features that are important to the economy. Numerous polygenic characteristics, including milk output, protein content, and fat, have been characterized at the genome level, and significant selection signatures have been found. The ability to uncover causative genes and variants linked to many phenotypes has been made possible in recent years by advancements in high-throughput genome scanning techniques, most notably whole-genome sequencing, SNP genotyping arrays, and comparative genomic hybridization (CGH) arrays. The next-generation sequencing method is an effective way of locating functional genes and genetic variations linked to crucial economic features in livestock when compared to the other two methods. The most significant economic qualities in the dairy industry are milk yield and composition, which are typical quantitative traits that are simultaneously regulated by many QTLs and polygenes. The cytochrome P450 enzymes can impact several dairy functions. Steroid 11-beta-hydroxylase is a mitochondrial enzyme that is produced using instructions from the *CYP11B1* gene. In cattle, it facilitates the conversion of 11-deoxy-cortisol to cortisol and 11-deoxycorticosterone to corticosterone. The protein produced by the bovine *CYP11B1* gene, which has nine exons and eight introns and is located on BTA14q12, is linked to the mitochondrial epithelium. The *CYP11B1* gene is located close to the marker ILSTS039, this marker is connected to milk characteristics. This makes the *CYP11B1* gene, along with milk yield and milk component yield, the functional and positional candidate gene for the milk production traits.

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Introduction

In the recent 40 years of development and progress the primary focus of animal biotechnology is to improve the milk and milk component yield.

The untiring effort has been put into improving the nutritional value of milk's component profile. The improvement of milk quality has always been a subject of concern because of its economic importance (Kale *et al.*, 2021). The most significant and valuable

livestock species for dairy production are thought to be cattle and buffalo. Many different livestock breeds are currently being utilized for value-added goods in the dairy sector. The adoption of the prevalent breed in each region of the world is prioritized to sustainably produce milk in that location (Kale *et al.*, 2021). To better understand molecular processes underlying the phenotypic manifestation of the milk production trait and to enhance the genomic assessment of milk-related traits, it is essential to identify genomic areas and candidate genes linked with the trait. The current review article focuses on the genetic processes underlying milk composition and production features, particularly concerning *CYP11B1* gene polymorphism investigations. The most significant component of milk's nutritional value is thought to be its fat content (Lock and Bauman, 2004). Raising the quality of milk is a goal of cattle breeding, in addition to boosting milk fat and protein levels (Kale *et al.*, 2021). The most significant and energizing component of milk is milk fat, and its content and composition are crucial benchmarks for assessing milk quality. The identification of useful candidate genes controlling milk fat is currently limited, though (Mu *et al.*, 2022).

It is critical to review genetic studies on dairy cattle to improve milk quality. Numerous genes have been investigated and discovered to be cooperatively involved in milk production features in dairy cattle, including *GAPD*, *RPS9*, *OXT*, *ACTB*, *GTP*, *ITGB4BP*, *Prolactin (PRL)*, *RPS23*, *POU1F1*, *RPS15*, *UXT*, *RAB11FIP1*, *DGAT1*, *SCD1*, *STAT5*, *ACSS2*, *AGPAT6*, *CYP11B1*, *PPARGC1A*, *CYP2U1*, *MRPS30*, *NIM1K*, *ZNF131*, *SLC4A4*, *ARHGAP39*, *PPP1R16A*, *FOXH1*, *KIFC2*, *CYHR1*, and *TONSL* etc. have been identified to play a role in milk production features (Wang *et al.*, 2020; Clancey *et al.*, 2019; Cai *et al.*, 2020; Jiang *et al.*, 2014).

The cytochrome P450 11 beta-hydroxylase 1 (*CYP11B1*) gene in cattle is the subject of our current review article. Due to *CYP11B1*'s function in steroid hormone synthesis in mammals, it is the significant candidate gene that affects the fat content of milk. The main goal of molecular genetics is to identify DNA polymorphisms that have an impact on the characteristics that are being bred in animals (Bionaz and Loor, 2008). The ability to conduct genome-wide association analyses employing PCR-RFLP and single nucleotide polymorphism (SNP) markers to find quantitative trait loci (QTL) relating to milk

production traits has been made possible by recent advances in molecular genetics (Bouwman *et al.*, 2012). Identification of SNPs in the candidate genes for milk characteristics is crucial given the advantages of genomic selection (Rahayu *et al.*, 2019). It's critical to maintain a balance between molecular genetic methods and traditional methods of animal breeding (Kale *et al.*, 2021).

The current study was also a modest attempt to investigate the genetic mechanism behind milk production traits with special reference to *CYP11B1* gene polymorphism studies around the world which is a highly desired and demanded attribute in the Asian region.

CYP11B1 gene structure and function

The *CYP11B1* gene was discovered and studied in humans, cattle, chickens, and rats (Amy *et al.*, 1990; Chirala *et al.*, 1997; Jayakumar *et al.*, 1994). By combining somatic cell hybrid (Cruz *et al.* 2019) analysis and fluorescence in-situ hybridization, the bovine *CYP11B1* gene was originally identified on chromosome BTA14q14 (Payne and Hales, 2004). The bovine *CYP11B1* gene has a 7716 base pair and has 9 exons and 8 introns (Figure 1) (GenBank Acc. No. NC_037341). (<http://www.ncbi.nlm.nih.gov/gene/282422>).

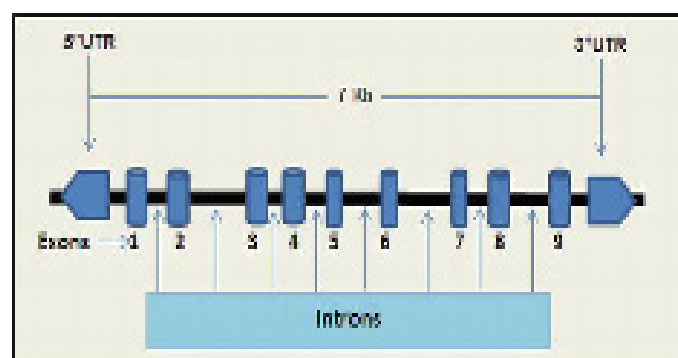


Figure 1: *CYP11B1* gene exon and intron arrangement (Ghaffar, 2019).

The inner mitochondrial membrane contains the *CYP11B1* enzyme. The *CYP11B1* enzyme which is also regarded as aldosterone synthase can catalyze three consecutive processes that all require one NADPH molecule, and one oxygen molecule in addition to the mitochondrial electron transport system to produce aldosterone from 11-deoxycorticosterone. The following are the three successive reactions: Aldosterone is created through the 11-hydroxylation of the 11-deoxycorticosterone via carbon 18

hydroxylation and the subsequent hydroxyl group oxidation of carbon 18 to produce the 18-C aldehyde group (Figure 3) (Boleckova *et al.*, 2012; Lisurek and Bernhardt, 2004).

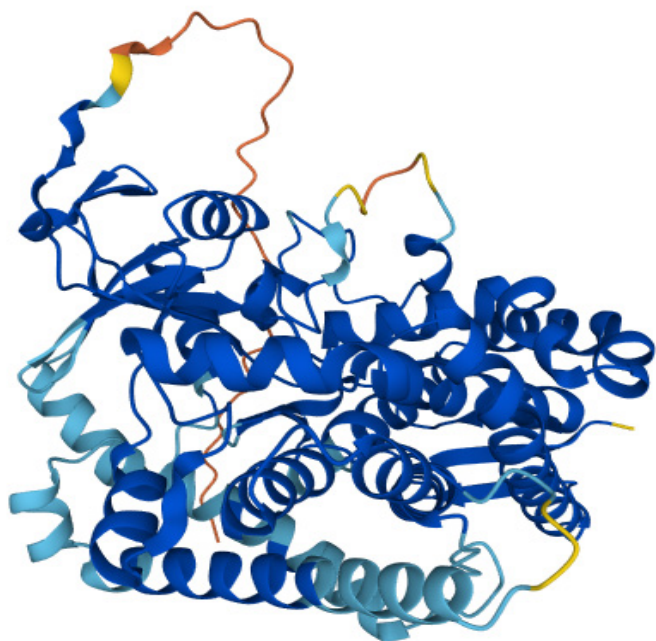


Figure 2: Protein structure of bovine *CYP11B1* (Ghfar, 2019).

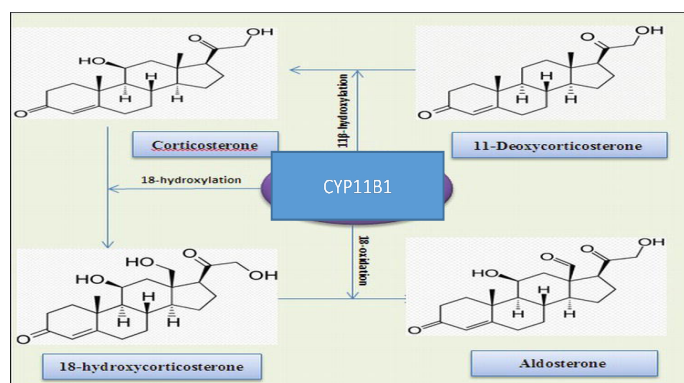


Figure 3: Reactions catalyzed via *CYP11B1* (Ghfar, 2019).

The *CYP11B1* gene greatly influences cortisol synthesis, androgen activity, and the number of milk gland cells that proliferate (Javed *et al.*, 2013). The major hormone that is involved in lipolysis and lipogenesis is still cortisol. The *CYP11B1* locus is now a prime target for association research and is of particular interest. In several breeds, the *CYP11B1* gene has been linked to milk production, energy metabolism, somatic cell score, and reproduction (Manzoor *et al.*, 2018).

CYP11B1 gene polymorphism studies using molecular techniques

Das *et al.* (2019) examined the Deoni cattle breed and revealed two genotypes, VV and VA, for the

putative exon 1 of the *CYP11B1* gene that were digested with the restriction enzyme PstI. Three band patterns mean VV genotypes, while four band patterns indicated VA genotypes. The observed frequencies of the VV and VA genotypes were 0.23 and 0.77, respectively, while the allelic frequencies for the V and A types were 0.62 and 0.38. In putative exon 1 of *CYP11B1*, sequence analysis discovered sixteen single nucleotide polymorphisms. The *CYP11B1* gene sequence was uploaded online to the NCBI gene bank and given the accession number KF471016 (Das *et al.*, 2019).

To better understand the biology behind milk production and give breeders the ability to alter milk fat content via genetic selection, Cruz *et al.* (2019) worked on the identification of genomic areas and potential genes related to milk fatty acids. They use a high-density (777K) SNP panel to undertake genome-wide association studies for five groups of milk fatty acids in Holstein cattle and suggest that the *CYP11B1* gene, a *CYHR1* paralogous that is related to milk fat in buffalo. Furthermore, according to Boleckova, a functional gene for traits associated with milk production in cattle is *CYP11B1*. However, the majority of genes with substantial impacts were found in the BTA14, adjacent to the *DGAT1* gene. This suggests that the *DGAT1* gene's effect may be influenced by a strong linkage disequilibrium with polymorphisms in the *DGAT1* gene which has been proven to be linked to milk fat content (Cruz *et al.*, 2019).

The bovine *CYP11B1* locus has a high level of overall sequence diversity, and 13 new polymorphisms were found. Seven of these were located in the coding region, while the other six were discovered in its intronic region. Genomic frequencies and allele distribution patterns were calculated for each SNP and HWE. SNPs that obey Hardy-Weinberg equilibrium were taken into account for linkage analysis. In this study, it was concluded that important polymorphisms in the *CYP11B1* gene, including V340L, T372D, T401M, and A415T, change the amino acids, and that polymorphism g.1305935 (T401M), which was discovered to be related with milk fat % (Manzoor *et al.*, 2018).

Another analysis by Javed *et al.* (2013) reported that the *CYP11B1* gene in Pakistani riverine buffalo breeds was sequenced to determine the genomic causes of

phenotypic diversity in dairy buffalo populations, particularly for milk yield traits. By analyzing the sequences of different buffalo groups having greater and lower fat contents, seven new SNPs were found (via an 8 % threshold value). Out of these versions of SNPs, only one was intronic. All of the remaining mutations, which caused amino acid alterations, were exonic and non-synonymous. These locations could be used to identify the causative mutation or neighboring QTL. However, breed-specificity was identified in polymorphic regions (Javed, 2016).

Javed (2016) aimed to predict protein-protein interactions in-silico for genes that are candidates for milk fat content in bovines. The prediction of a biological gene network was done followed by calculating the network interaction scores and determining the three-dimensional structure by applying PDB. Ten functional partners were identified through analysis of the *CYP11B1* network: *CYP11B2*, *CYP17A1*, *CYP19A1*, *HSD3B2*, *HSD17B6*, *HSD3B1*, *HSD17B3*, and *ENSG00000232414* (Figure 4). It was a network of closely linked nodes, and all of the associations were significant with high interaction score values. Along with this knowledge, 34 % homology of *CYP11B1* protein's three-dimensional structure was also estimated (Figure 2) (Javed, 2016).

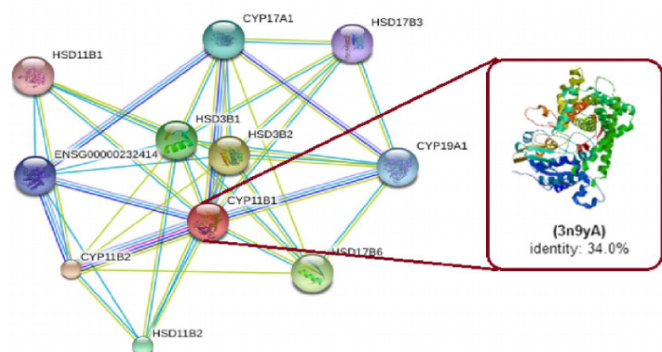


Figure 4: Network showing ten functional partners of *CYP11B1* involve in determining milk fat content; 3-D protein configuration prediction (Javed et al., 2014).

It was hypothesized that the gene responsible for the QTL associated with fat metabolism was located in the centromeric region of BTA14 (de Roos et al., 2007). It was found that the *CYP11B1* gene was positively correlated with fat content but negatively correlated with milk yield and protein yield. *CYP11B1* gene which has evolved into different isoforms in various species (Buelow et al., 1996; Mellon et al., 1995), although functional unity is retained in pigs, sheep, and cattle (Buelow et al., 1996). There are *CYP11B1*

pseudo genes in all animals (Mellon et al., 1995) . The *CYP11B1* gene can be regarded as a positional candidate gene because it has been localized to BTA14q12 and HSA8q21–23 (Kaupe et al., 2004). They suggest that *CYP11B1* is a potential candidate gene for milk yield as it's also involved in energy metabolism reported by (Mohammed et al., 2014).

Several additional genes, including *CYP11B1*, *MAPK15*, *VPS28*, *GPIHBP1*, *KCNK9*, *TRAPPC9*, and *CYHR1*, were also reported by Jiang et al. (2014) in addition to the *DGAT1* gene, which was verified in practically all association studies to have substantial connection with several milk production features. All of these genes were verified in their analysis, which also found that BAT14 has a considerable number of SNPs. It is thus highly likely that part of the effects are caused by linkage disequilibrium (LD) with the actual causal variations. We examined the levels of LD between each important SNP. On chromosomal BAT14, they reported SNPs in the *CYP11B1* gene at positions 2705205, 2708768, and 2706012 (Jiang et al., 2014).

Singh along with colleagues has reported the *CYP11B1* a potential gene for milk and milk production features. They found that there are 14 major milk proteins in cattle (Farrell et al., 2004), and they hypothesize that these proteins exhibit DNA-level variability, perpetuating a chemical change in the protein. However, the effects of each allele differ depending on the individual's genetic background and the experimental model (single locus vs. multi-locus effects). Several of them, including casein (Navani et al., 2002) and *CYP11B1* (Kaupe et al., 2007), have been demonstrated to be useful in determining the milk quality and lactation of dairy cattle and are commercially relevant (Singh et al., 2014).

BLAST was used to discover five polymorphic sites in the local Sahiwal breed. According to data, the exon one chromosomal locations 1310397, 1310450, 1310462, 1310487, and 1310519 had nucleotide changes in the following order: A>G, G>A, G>A, and A>G. The *CYP11B1* gene product has an Alanine (A) to Valine (V) polymorphism (V30A), which was discovered by a nucleotide substitution at position P1310487. Using the BioEdit translate tool, a link between the amino acid makeup of the reference and subject proteins was identified. Although the majority of identified SNPs do not change the sequence of

amino acids, these sites may be linked to surrounding QTLs and cause variants. The Sahiwal breed's allele distribution pattern and frequency patterns were found at specific polymorphic sites which depict breed specificity that is directly linked to milk yield traits (Manzoor *et al.*, 2013).

An experiment conducted by Javed *et al.* (2013) found 7 SNPs at the *CYP11B1* gene in the Pakistani Nili Ravi Buffalo breed. DNA was extracted from a variety of buffalo to look for polymorphism sites in the gene. Seven SNPs were found in an exonic region using the sequencing method. One of these SNPs was found to be silent, which didn't alter the amino acid. The remaining are significant in a way that they can change the amino acid sequence, which in turn can have an impact on the protein's structure and function (Javed *et al.*, 2013).

Boleckova and colleagues investigated allelic and genotypic frequencies of 5 DNA markers in Czech Fleckvieh cattle which are positional as well as functional candidates for the milk production traits. The *CYP11B1* gene has one of these markers. They assessed LD i.e. linkage disequilibrium between the 2 markers within the *PRL* (prolactin) gene and analyzed the correlation of the identified markers with breeding values associated with milk and milk production traits. 505 Czech Fleckvieh cows were genotyped in this investigation. In their investigation, segregation was confirmed by markers in *PPARGC1A*, *SPP1*, *CYP11B1*, and two polymorphisms in the *PRL* gene. They looked into the p.Val30Ala polymorphism in the *CYP11B1* first exon. *CYP11B1* gene polymorphism is positively associated with milk and milk production traits (Boleckova *et al.* 2012).

Some of the important economic traits like MY, FY, PY, FP, and PP major 10 SNP markers were selected for positional candidate gene searches within a flanking window of 1 Mb on either side of the marker. A semi-automated procedure that entailed acquiring and reviewing gene function predictions and publications for each gene and its orthologs in other species was used to choose functional candidate genes from the flanking areas. The genotyping data of GWAS related to milk yield from the BovineSNP50 Bead-Chip was used in this study. Over the entire genome, many potential and positional candidate genes for milk components were found. *CYP11B1* gene, which is located on chromosome BTA14, and

other previously identified genes having a significant influence on milk production traits (Li *et al.*, 2010).

Steroid 11-hydroxylase (cytochrome P450, subfamily XI B, polypeptide 1 (*CYP11B1*)) is a gene that encodes a steroid 11-beta-hydroxylase that converts 11-deoxycortisol to cortisol and 11-deoxycorticosterone to corticosterone, according to Boleckova *et al.* (2012). The ILSTS039 marker is close to the location of the *CYP11B1* gene on bovine chromosome 14. This marker is linked to milk production characteristics. This makes the *CYP11B1* gene, along with milk yield and milk component yield, a structural and positional candidate gene for milk traits. Ala/Ala, Ala/Val, and Val/Val genotype frequencies in the Czech Fleckvieh population were 0.07, 0.38, and 0.55, respectively. Hardy-Weinberg equilibrium existed in the *CYP11B1* gene's genotype distribution ($P = 0.05$), and the gene variation *CYP11B1A* was substantially related to increased MYBV ($P = 0.001$). Bovine *CYP11B1* gene Ala/Val polymorphism has a significant impact on milk output, breeding values for milk yield, and fat and protein contents in Czech Fleckvieh cows (Boleckova *et al.*, 2012).

Another study describes the *CYP11B1* gene as a potential gene for attributes related to milk production on the bovine chromosome 14, which has been thoroughly investigated for quantitative trait loci (QTL). Wibowo and his colleagues found 126 QTL by reviewing more than 40 studies that could be linked to genome assembly i.e. Btau 4.0. They discovered the region spanning 0–10 Mb on chromosome BTA14 in dairy cattle that have the highest density quantitative trait loci (QTL) map with a total 56 number of QTL, mostly for milk composition traits (Wibowo *et al.* 2008).

Another study was conducted to investigate the link between milk production and *CYP11B1* gene variants with the help of *CYP11B1* gene sequencing and other genetic tools. The exonic region of the bovine *CYP11B1* gene was amplified, sequenced, and genotyped by isolated genomic DNA samples and designing Primers of the targeted region. Less information is available about *CYP11B1* as a molecular marker on the genetic map at chromosome 14 which is why Kaupe *et al.* (2007) described little association of respective genes. The targeted region at *CYP11B1* gene product has an Alanine (A) to

Valine (V) polymorphism (V30A), due to nucleotide substitution at position P1310487 in the 5'UTR and exon 1 of the *CYP11B1* gene according to research results published by [Kaupe et al. \(2007\)](#). One of the genetic variability in the 5 UTR at exon 1 is strongly associated with the milk and milk components in German Holstein cattle ([Kaupe et al., 2007](#)).

The candidate gene approach is a powerful tool in genetic research and breeding programs and provides valuable insights into genes associated with specific traits based on prior knowledge of their biological function, to achieve a better understanding of the genetic basis of complex traits including milk production traits, livestock improvement, and disease management.

Conclusions and Recommendations

One of the probable candidate genes for milk production features and characteristic breeding values for MY, FY, FP, PY, and PP in various cattle breeds is the *CYP11B1* gene. The *CYP11B1* gene's DNA polymorphism research employing different molecular markers can be used to enhance the milk quality of dairy cattle. A thorough investigation of the gene's unstudied *CYP11B1* locus may also result in the discovery of several innovative and economically advantageous SNPs that will support breeding and selection decisions for the genetic advancement of dairy cattle. In light of these findings, the *CYP11B1* polymorphism has demonstrated favorable relationships with milk and milk composition traits such as MY (milk yield), PY (protein yield), and FY (fat yield) in several breeds of cattle ([Kale et al., 2021](#)). A possible marker for more productive and economical features can be employed with the identified polymorphism. A dependent evaluation of gene expression patterns will aid in our understanding of the biological mechanisms behind the *CYP11B1* gene along with its function in dairy animal production features. As a result, functional validation of *CYP11B1* gene polymorphisms should be carried out in the future ([Manzoor et al., 2018](#)).

Novelty Statement

This review explores the novel role of the *CYP11B1* gene in the regulation of milk production in cattle, offering insights into the genetic influence on milk production and ultimately providing a fresh

perspective on enhancing dairy productivity through genetic selection

Author's Contribution

Faheen Riaz: Conceptualization, methodology, writing original draft.

Sarfraz Mehmood: Review & editing, data curation.

Aatka Jamil and Khansa Jamil: Review & editing.

Imran Riaz Malik: Visualization, review & editing.

Muhammad Naeem Riaz: Supervision, project administration.

Ghulam Muhammad Ali: Resources.

Conflict of interest

The authors have declared no conflict of interest.

References

- Amy, C.M., B. Williams-Ahlf, J. Naggert and S. Smith. 1990. Molecular cloning of the mammalian fatty acid synthase gene and identification of the promoter region. *Biochem. J.*, 271(3): 675-679. <https://doi.org/10.1042/bj2710675>
- Animals, 2020. Cytochrome P450 Homepage. <https://drnelson.uthsc.edu/animals/>.
- Anwar, A., J.P. Coghlan and K. Jeyaseelanp. 2009. Structure of an Ovine *CYP11B1* Gene. *DNA Sequen.*, 8(6): 357-374. <https://doi.org/10.3109/10425179809020897>
- Barr, M., S.M. MacKenzie, D.M. Wilkinson, C.D. Holloway, E.C. Friel, S. Miller, T. MacDonald, R. Fraser, J.M.C. Connell and E. Davies. 2006. Functional effects of genetic variants in the 11-b-hydroxylase (*CYP11B1*) gene. *Clin. Endocrinol.*, 65(6): 816-825. <https://doi.org/10.1111/j.1365-2265.2006.02673.x>
- Bionaz, M. and J.J. Loo. 2008. Gene networks driving bovine milk fat synthesis during the lactation cycle. *BMC Genom.*, 9(1): 1-21. <https://doi.org/10.1186/1471-2164-9-366>
- Boleckova, J., J. Matejickova, M. Stipkova, J. Kyselova and L. Barton. 2012. The association of five polymorphisms with milk production traits in Czech Fleckvieh cattle. *Czech J. Anim. Sci.*, 57(2): 45-53. <https://doi.org/10.17221/5131-CJAS>
- Bouwman, A.C., M.H. Visker, J.A. van Arendonk and H. Bovenhuis. 2012. Genomic regions associated with bovine milk fatty acids in both

- summer and winter milk samples. BMC Genet., 13(1): 1-13. <https://doi.org/10.1186/1471-2156-13-93>
- Brown, N., P. Swart, G. Fenhalls, L. Stevens, N.W. Kolar and A.C. Swart. 2002. Baboon *CYP11B1*: The localization and catalytic activity in baboon adrenal tissue. Endocrine Res., 28(4): 477-484. <https://doi.org/10.1081/ERC-120016826>
- Buelow, K.L., W.J. Goodger, M.T. Collins, M.K. Clayton, K.V. Nordlund and C.B. Thomas. 1996. A model to determine sampling strategies and milk inoculum volume for detection of intramammary *Staphylococcus aureus* infections in dairy cattle by bacteriological culture. Prevent. Vet. Med., 25(3-4): 343-355.
- Cai, Z., M. Dusza, B. Guldbrandtsen, M.S. Lund and G. Sahana. 2020. Distinguishing pleiotropy from linked QTL between milk production traits and mastitis resistance in Nordic Holstein cattle. Genet. Sel. Evol., 52(1): 1-15. <https://doi.org/10.1186/s12711-020-00538-6>
- Chirala, S.S., W.Y. Huang, A. Jayakumar, K. Sakai and S.J. Wakil. 1997. Animal fatty acid synthase: Functional mapping and cloning and expression of the domain I constituent activities. Proc. Natl. Acad. Sci., 94(11): 5588-5593. <https://doi.org/10.1073/pnas.94.11.5588>
- Clancey, E., J.N. Kiser, J.G. Moraes, J.C. Dalton, T.E. Spencer and H.L. Neibergs. 2019. Genome-wide association analysis and gene set enrichment analysis with SNP data identify genes associated with 305-day milk yield in Holstein dairy cows. Anim. Genet., 50(3): 254-258. <https://doi.org/10.1111/age.12792>
- Cole, J.B., G.R. Wiggins, L. Ma, T.S. Sonstegard, T.J. Lawlor, B.A. Crooker, C.P. Van Tassell, J. Yang, S. Wang, L.K. Matukumalli and Y. Da. 2011. Genome-wide association analysis of thirty one production, health, reproduction and body conformation traits in contemporary U.S. Holstein cows. BMC Genom., 12(1). <https://doi.org/10.1186/1471-2164-12-408>
- Cruz, V.A., H.R. Oliveira, L.F. Brito, A. Fleming, S. Larmer, F. Miglior and F.S. Schenkel. 2019. Genome-Wide Association study for milk fatty acids in Holstein cattle accounting for the DGAT1 gene effect. Animals, 9(11): 997. <https://doi.org/10.3390/ani9110997>
- De Roos A.P.W., B.J. Hayes, R.J. Spelman and M.E. Goddard. 2008 Linkage disequilibrium and persistence of phase in Holstein-Friesian, Jersey and Angus cattle. Genetics, 179: 1503-12.
- Das, S.B. and U.T. Mundhe. 2019. CYP11B1 and PPARGC1A genes polymorphism controlling reproductive traits and estimation of breeding value of first lactation milk yield in *Bos indicus* (Deoni) cattle. Vet. Arhiv., 89(4): 463-479. <https://doi.org/10.24099/vet.arhiv.0340>
- El-Bayomi, K.M., I.E. El-Araby, A. Awad and A.W. Zagloul. 2015. Molecular study of some candidate genes affecting milk production traits in Holstein cattle. Alex. J. Vet. Sci., 45(1): 146. <https://doi.org/10.5455/ajvs.184431>
- Farrell Jr, H.M., R. Jimenez-Flores, G.T. Bleck, E.M. Brown, J.E. Butler, L.K. Creamer, C.L. Hicks, C.M. Hollar, K.F. Ng-Kwai-Hang and H.E. Swaisgood. 2004. Nomenclature of the proteins of cows' milk. Sixth revision. J. Dairy Sci., 87(6): 1641-1674. [https://doi.org/10.3168/jds.S0022-0302\(04\)73319-6](https://doi.org/10.3168/jds.S0022-0302(04)73319-6)
- Fontanesi, L., E. Scotti, A.B. Samorè, A. Bagnato and V. Russo. 2015. Association of 20 candidate gene markers with milk production and composition traits in sires of Reggiana breed, a local dairy cattle population. Livest. Sci., 176: 14-21. <https://doi.org/10.1016/j.livsci.2015.03.022>
- Gao, H., J. Xu, Q. Ma, F. Tang, Q. Ga, Y. Li, W. Guan, R.L. Ge and Y.Z. Yang. 2022. Association between the polymorphism of steroid hormone metabolism genes and high-altitude pulmonary edema in the Chinese Han population. Int. J. Gen. Med., 15: 787-794. <https://doi.org/10.2147/IJGM.S345495>
- Geldermann, H., 1975. Investigations on inheritance of quantitative characters in animals by gene markers I. methods. Theor. Appl. Genet., 46(7): 319-330. <https://doi.org/10.1007/BF00281673>
- Ghafar, M.T.A., 2019. Aldosterone synthase gene (CYP11B2) polymorphisms and enhanced cardiovascular risk. The recent topics in genetic polymorphisms, IntechOpen.
- Grisart, B., 2002. Positional candidate cloning of a QTL in dairy cattle: Identification of a missense mutation in the bovine *DGAT1* gene with major effect on milk yield and composition. Genome Res., 12(2): 222-231. <https://doi.org/10.1101/gr.224202>
- Grisart, B., F. Farnir, L. Karim, N. Cambisano, J.J. Kim, A. Kvasz, M. Mni, P. Simon, J.M. Frère,

- W. Coppieters and M. Georges. 2004. Genetic and functional confirmation of the causality of the *DGAT1 K232A* quantitative trait nucleotide in affecting milk yield and composition. *Proc. Natl. Acad. Sci.*, 101(8): 2398–2403. <https://doi.org/10.1073/pnas.0308518100>
- Hernández, N., J.C. Martínez-González, G.M. Parra-Bracamonte, A.M. Sifuentes-Rincón, N. López-Villalobos, S.T. Morris, F. Briones-Encinia, E. Ortega-Rivas, V.I. Pacheco-Contreras and L.A. Meza-García. 2016. Association of polymorphisms in growth hormone and leptin candidate genes with live weight traits of Brahman cattle. *Genet. Mol. Res.*, 15(3). <https://doi.org/10.4238/gmr.15038449>
- Hussain, M., H.N. Khan and F.R. Awan. 2018. Development and application of low-cost T-ARMS-PCR assay for AGT and *CYP11B1* gene polymorphisms. *Mol. Biol. Rep.*, 46(1): 443–449. <https://doi.org/10.1007/s11033-018-4493-0>
- Illa, S.K., S. Mukherjee, S. Nath and A. Mukherjee. 2021. Genome-wide scanning for signatures of selection revealed the putative genomic regions and candidate genes controlling milk composition and coat color traits in Sahiwal cattle. *Front. Genet.*, 12: 699422. <https://doi.org/10.3389/fgene.2021.699422>
- Imrie, H., M. Freel, B.M. Mayosi, E. Davies, R. Fraser, M. Ingram, H.J. Cordell, M. Farrall, P.J. Avery, H. Watkins, B. Keavney and J.M.C. Connell. 2006. Association between aldosterone production and variation in the 11 β -Hydroxylase (*CYP11B1*) gene. *J. Clin. Endocrinol. Metab.*, 91(12): 5051–5056. <https://doi.org/10.1210/jc.2006-1481>
- Javed, M., 2016. Study of candidate genes involved in milk production traits for identification of probable biomarkers in Nili-Ravi buffalo. Institute of biochemistry and biotechnology, University of Veterinary and Animal Sciences, Lahore.
- Javed, M., A. Nadeem, M.E. Babar and S. Manzoor. 2013. Single nucleotide polymorphisms in bovine *CYP11B1* gene in Nili Ravi buffalo breed of Pakistan. *Editorial Board.*, pp. 697.
- Jayakumar, A., S.S. Chirala, A. Chinault, Craig., A. Baldini, L. Abu-Elheiga and S.J. Wakil. 1994. Isolation and chromosomal mapping of genomic clones encoding the human fatty acid synthase gene. *Genomics*, 23(2): 420–424. <https://doi.org/10.1006/geno.1994.1518>
- Jiang, L., X. Liu, J. Yang, H. Wang, J. Jiang, L. Liu, S. He, X. Ding, J. Liu and Q. Zhang. 2014. Targeted resequencing of GWAS loci reveals novel genetic variants for milk production traits. *BMC Genom.*, 15(1): 1–9. <https://doi.org/10.1186/1471-2164-15-1105>
- Jiang, L., X. Liu, J. Yang, H. Wang, J. Jiang, L. Liu, S. He, X. Ding, J. Liu and Q. Zhang. 2014. Targeted re-sequencing of GWAS loci reveals novel genetic variants for milk production traits. *BMC Genom.*, 15(1). <https://doi.org/10.1186/1471-2164-15-1105>
- Kale, D.S., J. Singh, Y.B. Sathe and D.V. Patil. 2021. FASN gene and its role in bovine milk production.
- Kaupe, B., H. Brandt, E.M. Prinzenberg and G. Erhardt. 2007. Joint analysis of the influence of *CYP11B1* and *DGAT1* genetic variation on milk production, somatic cell score, conformation, reproduction, and productive lifespan in German Holstein cattle. *J. Anim. Sci.*, 85(1): 11–21. <https://doi.org/10.2527/jas.2005-753>
- Kaupe, B., S. Kollers, R. Fries and G. Erhardt. 2004. Mapping of *CYP11B* and a putative *CYHR1* paralogous gene to bovine chromosome 14 by FISH. *Anim. Genet.*, 35(6): 478–479. <https://doi.org/10.1111/j.1365-2052.2004.01200.x>
- Kim, S., B. Lim, J. Cho, S. Lee, C.G. Dang, J.H. Jeon, J.M. Kim and J. Lee. 2021. Genome-wide identification of candidate genes for milk production traits in Korean Holstein cattle. *Animals*, 11(5): 1392. <https://doi.org/10.3390/ani11051392>
- Kumbhar, A.S., H. Magsi, M.I. Kumbhar and Z.K. Rind. 2018. Status of population growth and food sustainability in Pakistan. *Indian J. Sci. Technol.*, 11(16): 211–223. <https://doi.org/10.17485/ijst/2018/v11i16/119048>
- Li, H., Z. Wang, S.S. Moore, F.S. Schenkel and P. Stothard. 2010. Genome-wide scan for positional and functional candidate genes affecting milk production traits in Canadian Holstein Cattle. *Proc. 9th WCGALP*, Leipzig, Germany, pp. 26.
- Li, H., Z. Wang, S. Moore, F. Schenkel and P. Stothard. 2010. Genome-wide scan for positional and functional candidate genes

- affecting milk production traits in Canadian Holstein cattle. *J. Med. Genet.*, 37(11): 831–835.
- Li, Q., R. Liang, Y. Li, Y. Gao, Q. Li, D. Sun and J. Li. 2020. Identification of candidate genes for milk production traits by RNA sequencing on bovine liver at different lactation stages. *BMC Genet.*, 21(1): 1–12. <https://doi.org/10.1186/s12863-020-00882-y>
- Li, Q., R. Liang, Y. Li, Y. Gao, Q. Li, D. Sun and J. Li. 2020. Identification of candidate genes for milk production traits by RNA sequencing on bovine liver at different lactation stages. *BMC Genet.*, 21(1). <https://doi.org/10.1186/s12863-020-00882-y>
- Lin, J.H., K.Y. Peng, Y.P. Kuo, H. Liu, C.M.B. Tan, Y.F. Lin, H.W. Chiu, Y.H. Lin, Y.M. Chen, J.S. Chueh and V.C. Wu. 2022. Aldosterone-producing nodules and *CYP11B1* signaling correlate in primary aldosteronism. *Endocrine-Related Cancer*, 29(2): 59–69. <https://doi.org/10.1530/ERC-21-0287>
- Lock, A.L. and D.E. Bauman. 2004. Modifying milk fat composition of dairy cows to enhance fatty acids beneficial to human health. *Lipids*, 39(12): 1197–1206. <https://doi.org/10.1007/s11745-004-1348-6>
- Ma, Y., M.Z. Khan, J. Xiao, G.M. Alugongo, X. Chen, T. Chen, S. Liu, Z. He, J. Wang, M.K. Shah and Z. Cao. 2021. Genetic markers associated with milk production traits in dairy cattle. *Agriculture*, 11(10): 1018. <https://doi.org/10.3390/agriculture11101018>
- Mai, M.D., G. Sahana, F.B. Christiansen and B. Guldbrandtsen. 2010. A genome-wide association study for milk production traits in Danish Jersey cattle using a 50K single nucleotide polymorphism chip1. *J. Anim. Sci.*, 88(11): 3522–3528. <https://doi.org/10.2527/jas.2009-2713>
- Manzoor, S., A. Nadeem, M. Javed and M.E. Babar. 2013. Identification of single nucleotide polymorphism in 5'-UTR of *CYP11B1* gene in Pakistani Sahiwal cattle. *Indian J. Biochem. Biophys.*, 7(10): 995–997.
- Manzoor, S., A. Nadeem, J. Maryam, M.E. Babar, T. Hussain and Z.I. Rajput. 2018. Polymorphism in steroid 11-beta-hydroxylase gene effects on milk fat content in Sahiwal cattle. *J. Anim. Plant Sci.*, 28(2): 456–459.
- Marques, E., R.D. Schnabel, P. Stothard, D. Kolbehdari, Z. Wang, J.F. Taylor and S.S. Moore. 2008. High density linkage disequilibrium maps of chromosome 14 in Holstein and Angus cattle. *BMC Genet.*, 9(1). <https://doi.org/10.1186/1471-2156-9-45>
- Marques, E., R.D. Schnabel, P. Stothard, D. Kolbehdari, Z. Wang, J.F. Taylor and S.S. Moore. 2008. High density linkage disequilibrium maps of chromosome 14 in Holstein and Angus cattle. *BMC Genet.*, 9(1): 1–12. <https://doi.org/10.1186/1471-2156-9-45>
- Meignanalakshmi, S. and Mahalinga-Nainar, 2009. PCR-RFLP analysis of beta-lactoglobulin gene in murrah buffaloes. *Tamilnadu J. Vet. Anim. Sci.*, 5(5): 194–197.
- Mellon, S.H., S.R. Bair and H. Monis. 1995. P450c11B3 mRNA, transcribed from a third P450c11 gene, is expressed in a tissue-specific, developmentally, and hormonally regulated fashion in the rodent adrenal and encodes a protein with both 11-hydroxylase and 18-hydroxylase activities. *J. Biol. Chem.*, 270(4): 1643–1649.
- Missohou, A., E. Talaki and I.M. Laminou. 2006. Diversity and genetic relationships among seven West African goat breeds. *Asian Austral. J. Anim. Sci.*, 19(9): 1245. <https://doi.org/10.5713/ajas.2006.1245>
- Mohammed, S.A., S.A. Rahamtalla, S.S. Ahmed, A. Elhafiz, B.M. Dousa, K.M. Elamin and M.K.A. Ahmed. 2015. DGAT1 gene in dairy cattle. *Glob. J. Anim. Sci. Res.*, 3(1): 191–198.
- Mu, T., H. Hu, Y. Ma, H. Wen, C. Yang, X. Feng, W. Wen, J. Zhang and Y. Gu. 2022. Identifying key genes in milk fat metabolism by weighted gene co-expression network analysis. *Sci. Rep.*, 12(1): 1–13. <https://doi.org/10.1038/s41598-022-10435-1>
- Mukai, K., M. Imai, H. Shimada and Y. Ishimura. 1993. Isolation and characterization of rat *CYP11B* genes involved in late steps of mineralo- and glucocorticoid syntheses. *J. Biol. Chem.*, 268(12). [https://doi.org/10.1016/S0021-9258\(18\)52987-2](https://doi.org/10.1016/S0021-9258(18)52987-2)
- Mukangwa, M., K. Takizawa, Y. Aoki, S. Hamano and M. Tetsuka. 2020. Expression of genes encoding mineralocorticoid biosynthetic enzymes and the mineralocorticoid receptor, and levels of mineralocorticoids in the bovine follicle and corpus luteum. *J. Reprod. Dev.*, 66(1): 75–81. <https://doi.org/10.1262/>

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- Mwangi, S.I. and E.D. Ilatsia. 2022. Sahiwal breed in pastoral production systems in Kenya: Future roles and existing gaps in knowledge and supportive technical logistics. A review.
- Nanaei, H.A., M.A. Edriss, S.A. Mahyari, H.R. Rahmani and B.F.S. Tabatabaei. 2012. *Lactoferrin* gene polymorphism of Holstein cows in Isfahan province. *Biotechnology*, 7(2).
- Navani, N., P.K. Jain, S. Gupta, B.S. Sisodia and S. Kumar, 2002. A set of cattle microsatellite DNA markers for genome analysis of riverine buffalo (*Bubalus bubalis*). *Ani. Gen.*, 33(2): 149-154.
- Näslund, J., W.F. Fikse, G.R. Pielberg and A. Lundén. 2008. Frequency and effect of the bovine *Acyl-CoA: diacylglycerol acyltransferase 1 (DGAT1) K232A* polymorphism in Swedish dairy cattle. *J. Dairy Sci.*, 91(5): 2127–2134. <https://doi.org/10.3168/jds.2007-0330>
- Noorisadegh, M., S. Ansari-Mahyari, P.M.E. Nasab and F. Rafeie. 2018. Quantitative trait loci affecting milk production traits on BTA 14 in Iranian Holstein dairy cattle: A confirmation. *Iran. J. Appl. Anim. Sci.*, 7(4): 607–614.
- Pasha, T.N. and Z. Hayat. 2012. Present situation and future perspective of buffalo production in Asia. *J. Anim. Plant Sci.*, 22(3): 250–256.
- Payne, A.H. and D.B. Hales. 2004. Overview of steroidogenic enzymes in the pathway from cholesterol to active steroid hormones. *Endocrine Rev.*, 25(6): 947-970. <https://doi.org/10.1210/er.2003-0030>
- Peter, M., J.M. Dubuis and W.G. Sippell. 1999. Disorders of the aldosterone synthase and steroid 11 β -hydroxylase deficiencies. *Horm. Res. Paediat.*, 51(5): 211–222. <https://doi.org/10.1159/000023374>
- Plante, Y., J.P. Gibson, J. Nadesalingam, H. Mehrabani-Yeganeh, S. Lefebvre, G. Vandervoort and G.B. Jansen. 2001. Detection of quantitative trait loci affecting milk production traits on 10 chromosomes in Holstein cattle. *J. Dairy Sci.*, 84(6): 1516–1524. [https://doi.org/10.3168/jds.S0022-0302\(01\)70185-3](https://doi.org/10.3168/jds.S0022-0302(01)70185-3)
- Rahayu, A.P., T. Hartatik, A. Purnomoadi and E. Kurnianto. 2019. Association of single nucleotide polymorphisms in the fatty acid synthase, LOC514211, and fat mass and obesity-associated genes with milk traits in Indonesian-Holstein dairy cattle. *Vet. World*, 12(7): 1160. <https://doi.org/10.14202/vetworld.2019.1160-1166>
- Rehman, A., L. Jingdong, A.A. Chandio and I. Hussain. 2017. Livestock production and population census in Pakistan: Determining their relationship with agricultural GDP using econometric analysis. *Inf. Proc. Agric.*, 4(2): 168–177. <https://doi.org/10.1016/j.inpa.2017.03.002>
- Rehman, A., L. Jingdong, A.A. Chandio and I. Hussain. 2017. Livestock production and population census in Pakistan: Determining their relationship with agricultural GDP using econometric analysis. *Inf. Process. Agric.*, 4(2): 168-177. <https://doi.org/10.1016/j.inpa.2017.03.002>
- Riaz, M.N., N.A. Malik, F. Nasreen and J.A. Qureshi. 2008. Molecular marker assisted study of kappa casein gene in nili-ravi (Buffalo) breed of Pakistan. *Pak. Vet. J.*, 28(3): 103–106.
- Riaz, M.N., N.A. Malik, F. Nasreen, J.A. Qureshi and S.U.H. Khan. 2011. Genetic variability in the kappa-casein gene in Sahiwal, Cholistani and Red Sindhi cattle breeds. *Int. J. Dairy Technol.*, 65(2): 208–211. <https://doi.org/10.1111/j.1471-0307.2011.00755.x>
- Riaz, M.N., N.A. Malik, F. Nasreen, J.A. Qureshi and S.U.H. Khan. 2012. Genetic variability in the kappa-casein gene in Sahiwal, Cholistani and Red Sindhi cattle breeds. *Int. J. Dairy Technol.*, 65(2): 208-211. <https://doi.org/10.1111/j.1471-0307.2011.00755.x>
- Schiffer, L., S. Anderko, A. Hobler, F. Hannemann, N. Kagawa and R. Bernhardt. 2015. A recombinant *CYP11B1* dependent *Escherichia coli* biocatalyst for selective cortisol production and optimization towards a preparative scale. *Microb. Cell Factor.*, 14(1). <https://doi.org/10.1186/s12934-015-0209-5>
- Shahbandeh, M., 2024. Global cow milk production 2015-2023. <https://www.statista.com/statistics/263952/production-of-milk-worldwide/>.
- Singh, U., R. Deb, R.R. Alyethodi, R. Alex, S. Kumar, S. Chakraborty, K. Dhama and A. Sharma. 2014. Molecular markers and their applications in cattle genetic research: A review. *Biomark. Genom. Med.* 6(2): 49-58.
- Tambasco, D.D., C.C.P. Paz, M. Tambasco-Studart, A.P. Pereira, M.M. Alencar, A.R. Freitas, L.L. Couninho, I.U. Packer and L.C.A. Regitano.

2003. Candidate genes for growth traits in beef cattle crosses *Bos taurus* x *Bos indicus*. J. Anim. Breed. Genet., 120: 51-56. <https://doi.org/10.1046/j.1439-0388.2003.00371.x>
- Thornton, P.K., 2010. Livestock production: Recent trends, future prospects. Trans. R. Soc. B, 365(1554): 2853-2867. <https://doi.org/10.1098/rstb.2010.0134>
- Wang, T., Li, J., Gao, X., Song, W., Chen, C., Yao, D., Ma, J., Xu, L. and Ma, Y., 2020. Genome-wide association study of milk components in Chinese Holstein cows using single nucleotide polymorphism Livestock Science., 233: 103951. <https://doi.org/10.1016/j.livsci.2020.103951>.
- Wibowo, T.A., C.T. Gaskins, R.C. Newberry, G.H. Thorgaard, J.J. Michal and Z. Jiang. 2008. Genome assembly anchored QTL map of bovine chromosome 14. Int. J. Biol. Sci., 4(6): 406. <https://doi.org/10.7150/ijbs.4.406>