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Significance of Butyrophilin Gene in Relation to Milk Constituents in Dairy Animals

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Abstract
Butyrophilin (BTN1A1) has been classified as member of transmembrane proteins of immunoglobulin family. BTN1A1 is a QTL candidate gene having role in milk production and composition (fat) in dairy animals. The gene product BTN1A1 has function during secretion of milk fat and its expression is tissue specific in lactating mammary tissue. Butyrophilin gene constitutes of a more than 40% by weight of total protein and synthesized as a peptide comprised of 526 amino acids. Hydrophobic sequence gets cleaved before secretion in association with milk fat globule membrane (MFGM). Cholesterolemia-lowering factor, inhibitors of cancer cell growth, vitamin binders and inhibitor of various bacterial diseases are different health favorable components of MFGM. The gene frequency of polymorphism in BTN1A1 gene has been found to vary among dairy animals. In dairy animals, several studies revealed association of BTN1A1 gene with high milk yield, fat content and protein yield. These associations suggest gene polymorphisms or genetic variability that can be further utilized for selecting superior dairy animals.

Keywords: *bovine**,** butyrophilin, milk fat globule membrane (MFGM), milk fat secretion*

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INTRODUCTION

Goal of any dairy business has been to identify an effective way of increasing milk production and its constituents (fat and protein) without increasing the size of dairy herd, i.e., improving productivity and quality of milk. Selection of superior dairy animals with desirable genotypes and mating them to produce next generation has been the basis of livestock improvement; and this would continue to remain same in the coming years in India. Identification of genetic markers is a promising technique which can strengthen the current conventional breeding methods for quantitative trait selection. Once these variations identified in genes are proven to be associated with quantitative traits of interest, it may accelerate the genetic gain in dairy animals.

Numbers of single nucleotide polymorphisms (SNPs) have shown positive and significant associations with milk fat secretion among different breeds of milch bovines. Milk fat is a major contributor to energy density of whole milk and affects the physical and manufacturing properties of various dairy products. Fat content or fat percentage in milk is genetically variable in an animal and many environmental and physiological factors also affect milk fat secretion in milch bovine. Quantitative traits of economic importance in livestock have a complex genetics. Moreover, selection intensity with respect to certain quantitative traits is relatively higher through indirect selection, such as potential candidate gene or marker-based approach [1] and thus overall genetic progress can be improved for desired trait at a considerably higher rate.

Genetic research in dairy animals focuses mostly on identification of genes affecting economically important traits that could be useful in breeding programs for selection of superior animals [2]. Genetic variation or polymorphism is raw material for improvement of animals and can be studied at phenotypic as well as genetic level. The expression of characters is governed by certain genes (potential candidate gene) so identification of those genes is important to study genetic variations or polymorphism for faster and effective genetic improvement of animals. The concept of potential candidate gene approach helps to identify the gene responsible for significant variation in certain trait. With use of various molecular technologies developed for identification and characterization of potential candidate genes it may be possible to select a breeding animal for an extensive range of traits and to enhance reliability in predicting mature phenotype of individual. In India, breeding policies for dairy animals (cattle and buffalo) must focus not only on increasing milk yield but also on milk composition and its quality, such as fat percent and protein percentage in milk. It has economical aspect associated with it as in organized sectors and at dairy cooperatives, livestock owners are paid on the basis of fat corrected milk (fat percentage) [3]. Moreover, many producer companies are ready to pay premium for milk rich in fat content thus encouraging livestock keepers particularly buffalo keepers to improve fat content in milk.

However, in bovines, fat percent and milk yield is negatively correlated but genetic selection for higher fat yield could improve the dairy income. Genetic gain is proportional to the amount of genetic variability present in a population or herd. Recent studies in exotic cattle have revealed large genetic variations in bovine milk fat and fat associated genes [4, 5] and many single nucleotide variations or polymorphism among these potential candidate genes play an important role in fat synthesis or have been associated with fat percentage or fat yield in milk. Such candidate genes for fat synthesis includes fatty acid synthase (FASN) gene [6–10], Oxidized low density lipoprotein receptor-1 (*OLR1*) gene [11, 12], Diacylglycerol-acyl-transferase-1 (*DGAT1*) gene [13, 14], Signal transducer and activator of transcription-1 (*STAT1*) gene [15–17].

The genetic improvement over a period of time can be increased by incorporating these potential candidate gene markers in selection programmes for selection of dairy animals. Information from SNPs linked to QTL can be used to improve selection for milk and milk constituent (fat) traits. The genetic variations or polymorphism in bovine *BTN1A1* gene has been exploited as a marker for QTL controlling milk yield and fat percentage [18] as well as somatic cell count [19, 20].

BTN1A1 is a potential candidate gene which is very crucial for milk yield and its composition (fat). BTN1A1 is a QTL candidate that affects traits mainly milk yield and fat percentage in dairy animal because it is mainly expressed in lactating mammary tissue and gene product BTN1A1 function in secretion of milk fat in milk [21]. Many research has confirmed definite function of BTN1A1 in fat secretion [22–24] and disease resistance [25, 26]. It has also been proved that amount of bovine BTN1A1 gene expression increases exponentially during last 6 weeks of pregnancy in bovines, specifically in the lactating mammary epithelial tissue [27, 28]. This gene expression is regulated at transcription level by lactogenic hormones in lactating dairy animals [22]. It is a type 1 transmembrane glycoprotein placed between plasma membrane and surface of lipid droplets synthesized from 526 amino acids and conserved in B30.2 domain in the cytoplasmic tail. It was identified as a principal component of milk fat globule membrane (MFGM) that is important in secreting and stabilizing milk fat droplets in milk of lactating dairy animals.

Butyrophilin is a family of proteins and a protein associated with milk fat droplets, is directly involved in secretion of fat globules during lactation at the apical surface of mammary epithelial cells in lactating dairy animals [29]. Polymorphisms at DNA level contributes to genetic characterization of livestock and poultry population. Polymorphisms in exonic region of a gene may lead to change in amino acids which change the expressed protein [30]. Secretion of fat globule in milk is primarily based on getting proper shape of fat droplets and butyrophilin plays vital role during the process of lactogenesis in lactating dairy animals [31].

Butyrophilin genes organize a subgroup of about ten genes in the Ig superfamily recognized in cattle, goat and other species. BTN1A1 is most abundant protein in milk fat globule membrane and is specifically expressed in lactating mammary tissue in dairy animals. It is produced in the end of pregnancy and is maintained throughout lactation [23]. About more than 40% by weight of the total protein associated with fat globule membrane of bovine milk is constituted by this protein

[32]. Butyrophilin (BTN) protein is usually sandwiched between plasma membrane and surface of fat droplets and is insoluble in nonionic detergent [33] because of its hydrophobic property. During budding and secretion of fat droplets into milk, this protein is integrated into the milk-fat-globule membrane. Though, butyrophilin may function as an integral receptor for cytoplasmic fat droplets but budding of droplets at the cell surface is initiated by interactions between cytoplasmic tail of BTN along with other proteins such as GTP-binding proteins and fat [29]. Butyrophilinhas structural similarities with the proteins of immune system suggesting its possible immunologic function unrelated to milk fat secretion in milk of lactating animals [34]. Several mammalian species including cattle [29], human [35] and mice [36] have BTN1A1 gene. The bovine Butyrophilin gene, 7003 bp long gene fragment, is located at chromosome 23 consisting of 8 exon and 7 intron [18, 37]. BTN1A1 is probably QTL candidate that affects an economically important trait in dairy animals including milk yield and milk composition [20]. Franke et al. [38] recommended that butyrophilin gene is specific to mammary tissue and expressed extensively during lactation in dairy animals.

Butyrophilin is a glycoprotein having 66-67 kDa molecular weight and consisting of an N-terminal exoplasmic domain with 2 Ig like folds and a C-terminal cytoplasmic domain which is involved in interactions with other proteins [39, 40]. Cattle and buffaloes Butyrophilin consists of 526 amino acids having near about 56 kDa molecular weight and first 26 of them constitute a signal peptide [29]. Butyrophilin protein shows a domain character and is strongly associated with the cell membrane [29].

FUNCTION OF BUTYROPHILIN GENE

Butyrophilin is main protein associated with lipid droplets in the milk. Milk fat droplets in lactating cattle and buffalo is secreted in udder in the form of microlipid droplets which are surrounded by a special membrane consist of lipid bilayer and proteins. This special membrane has been designated as milk fat globule membrane and is important

in the secretion and stabilization of milk fat droplets in milk of dairy animals. In the milk of Holstein Friesian and Jersey cows, out of total milk fat globule membrane proteins approximately 34–43% and 20% is comprised by this layer, respectively [27]. In the past decade, there is extensive increase in knowledge of intracellular origin of lipid droplets, the identity and potential function of MFGM proteins in milk lipid secretion and molecular determinants involved in the process of lipogenesis [27, 41, 42]. Butyrophilin plays a significant role in attainment of proper shape of fat droplets during lactogenesis which is critical for secretion of fat globules in milk of dairy animals [24, 43].

It was observed that increase of butyrophilin is related with onset of milk fat droplets secretion towards the end of pregnancy and is sustained throughout lactation of lactating animals [22]. Location of butyrophilin protein within the cell, domain structure of protein and site-specific expression occurring only during lactation in lactating animal indicate that butyrophilin protein is of great importance in milk lipid droplets secretion process by directing the extrusion process of milk fat globules in milk [23, 44, 45]. It has been postulated that specific interaction between BTN and XO is required to form signaling complex. These observations were based on the expression profiles of butyrophilin (BTN1A1) and Xanthine Oxidoreductase (XO) during pregnancy as well as lactation and the phenotypes of Btn-- and Xo+/- in mice.

Formation of a complex known as ‘supramolecular complex’ among butyrophilin and XO proteins with other proteins on the surface of cytoplasmic fat droplets. The association of milk fat globule membrane and subsequent expulsion of fat droplets from the cell is dependent on this complex [46, 47]. Several workers [24] proposed an alternative that milk fat globule secretion is controlled by interactions between plasma membrane and butyrophilin in secretory granule phospholipid monolayer.

These results strongly highlight that butyrophilin protein function in secretion of fat droplets. Practically, these results highlight the importance milk fat globule membrane in stabilizing fat droplets in cattle and buffalo milk and consequences occur due to disruption of this membrane. BTN1A1 gene is therefore a potential candidate to be incorporated in genetic screening of dairy cattle for milk quality like fat and protein yield and production traits which have economic importance [44].

GENETIC VARIABILITY OF *BTN1A1* GENE IN RELATION TO MILK CONSTITUENTS IN BOVINE

According to Taylor *et al*. [34], out of two alleles present in Holstein Friesian cattle, highest frequency was found in AA genotype and A allele was predominant, whereas lowest frequency was found for BB genotype. Such type of polymorphic information in other milk protein genes were also reviewed in cattle and yak by Badola *et al*. [48] and Mao *et al*. [49], respectively.

Pareek et al. [50] reported allele variants or polymorphism of BTN1A1 encoding gene with milk production traits like milk yield and milk constituent's traits in cattle. They reported a significant association between protein sequence polymorphism and milk fat percentage.

Jang et al. [51] reported that BTN3 was associated with 305-day production traits ($p<0.05$) after observing the association of butyrophilin candidate genes with production traits in Korean dairy proven and young bulls.

In crossbred cattle, Bhattacharya et al. [57] observed HaeIII PCR- RFLP polymorphism and reported three genotypes viz., AA, BB and AB having substantial effects on total milk solid, fat and SNF percentages.

Komisarek et al. [20] analyzed relationship between two SNPs of BTN1A1 gene in exons 3 and 8 in cattle. They detected the AA genotype was characterized by significantly higher milk, fat, and protein yields than AG and GG genotypes in cattle.

Sadr et al. [52] reported genetic variations of BTN1A1 gene in Najdi cattle through PCR-RFLP method and found that exon 8 of butyrophilin gene was polymorphic. In Jersey cattle, Magdalena et al. [53] reported associations between two polymorphisms localized in 7 exon of butyrophilin gene (BTN1A1/HaeIII and BTN1A1/SchI) with milk production traits which are economic importance and revealed that GG/AG combined genotype was characterized by a significant lower fat percentage in comparison to other combinations.

Rangarajan [54] reported genetic variability of exon 8 and exon 3 of butyrophilin gene and its association with milk production traits and SCC in Holstein Friesian crossbred cattle and Deoni cattle. They observed that there was no association between total daily fat percentage and BTN1A1 genotypes in Holstein Friesian crossbred and Deoni cattle for exon 3. However, for exon 8 they observed that in Holstein Friesian crossbred and Deoni cattle with AA genotype had a higher milk fat percentage and animals with BB genotype had lower values of milk fat percentage in Holstein Friesian crossbred and Deoni cattle.

Yardibi *et al.* [55] studied *BTN1A1* gene polymorphism in East Anatolian red cattle breed and South Anatolian red cattle breed. They observed three genotypes following amplification of a region of *BTN1A1* gene. The overall frequency of A allele was significantly higher than that of B allele.

Kale et al. [56] reported association of butyrophilin candidate gene in Murrah buffaloes and found that BB genotypes had higher milk yield as compared to AA and CC genotypes.

CONCLUSION

BTN1A1 is an important potential gene for milk yield and milk fat. Polymorphism of *BTN1A1* gene has been associated with both milk yield and its composition traits; as well as plays a significant role in regulating milk fat secretion. In organized sectors and dairy cooperatives, livestock owners are generally paid on the basis of fat corrected milk. Thus, selection of dairy animals for BTN1A1 could be a major deterrent in improving dairy economics.

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