



Potential candidate gene markers for milk fat in bovines: A review

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ABSTRACT

In dairy animals, the principal goal of selection is to improve quality and quantity of milk. Genetic information inferred from single nucleotide polymorphism (SNP) primarily linked to Quantitative Trait Loci (QTL) can be used to improve selection for milk and milk constituent traits in bovines. Selection for a marker allele known to be associated with a beneficial QTL increases the frequency of that allele and hence, dairy performance can be enhanced. One of the potential benefit of selection based on molecular marker is that the marker genotypes can be determined in a dairy animal just after birth. Thus, marker information can be used to predict an animal's genotype before its actual performance recording for a trait is available, which considerably reduces generation interval and thus improves genetic gain in a herd for milk and its constituent traits. This review article is an attempt to comprehend the idea behind marker based selection for milk fat and genes regulating milk fat with significant effects that can be targeted specifically in selection of superior dairy animals. Once an association is established, it can be utilized in a marker assisted breeding program for improvement of bovines.

Keywords: Fat associated genes, Marker assisted selection, Milk fat, Polymorphism

India is endowed with vast genetic resources of bovines with an estimated number of 302.79 million including 192.49 million cattle and 109.85 million buffalo population (Livestock Census 2019) and 50 recognized breeds of cattle and 17 recognized breeds of buffaloes present in various states of the country (NBAGR 2020). Milk production of India during 2016–17 was 165.4 million tonnes and in 2017–18, it reached 176.3 million tonnes showing an annual growth rate of 6.62% (DAHD 2018–19).

In India, breeding strategies for dairy animals must have emphasis not only on increasing production performance (milk yield), but also on milk composition and its quality like fat percent in milk. This has an economic importance because in organized sectors and dairy co-operatives, livestock owners are remunerated on the basis of fat percentage or fat corrected milk (FCM). Additionally, many milk processing companies are willing to pay the premium for milk rich in fat content, thus encouraging livestock keepers to improve the fat content in milk. However, in dairy animal's, fat percent and milk quantity are negatively correlated to each other, but genetic selection for higher fat yield could improve the dairy economics. Genetic gain is proportional to the amount of genetic variation present in a population and more genetic variation exists for fat yield as compared to fat percentage. Thus, in order to get more genetic gain, selection of dairy animals should be done based on fat yield as compared to fat percentage. Kumar *et al.* (2016a) reported that in 5th monthly test day estimates of phenotypic and

genetic correlations of monthly test day fat yield with 305-day fat yield was generally higher suggesting that this test day yields could be used as selection criteria for early evaluation and selection of Murrah buffaloes.

It is important to balance molecular genetic techniques with conventional animal breeding methodologies to improve the animal breeding program (Barillet *et al.* 2007). Development in the field of molecular biology involves the use of molecular markers for improvement of production traits including fat yield or fat percentage in bovines. Markers are mainly of 4 types, viz. morphological, biochemical, cytological and molecular or DNA markers. Molecular marker is defined as a DNA fragment or small portion of DNA which is present at a certain location in the genome and is associated with particular traits. Molecular markers have umpteen number of applications like parentage and twin zygosity determination, estimation of genetic distance, identification of disease carrier individuals, marker-assisted selection, gene mapping etc. Soyeurt *et al.* (2007) and Stoop *et al.* (2008) reported extensive genetic variations in bovine milk and milk fat genes and stated that many single nucleotide variations (SNP) among potential candidate genes play a specific role in fat synthesis or have been associated with fat percentage or fat yield in milk.

Marker-assisted selection for quantitative traits like fat yield followed with appropriate breeding methods can enable fast genetic gains under various bovine breed improvement programmes (Erhardt and Weimann 2007). In India, dairy animals are not selected based on molecular markers related to fat percentage or fat yield. Present review

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deals with the numerous molecular markers associated with fat percentage or fat yield in the selection of superior animals for better milk fat production in bovine (cattle and buffaloes).

Numbers of single nucleotide polymorphisms (SNPs) have shown positive and significant associations with milk

fat secretion among different breeds of cattle and buffaloes. Information from SNPs linked to QTL can be used to improve selection for milk and milk constituent (fat) traits. Candidate genes studied for the association with milk fat in cattle and buffaloes, their location, SNPs and their association are given in Table 1.

Table 1. Important milk fat associated potential candidate gene markers in bovines

Gene	*Chr.	Function	SNP	Association	References
FASN	19	Fatty acid synthase	Exon 1 and 34	Significantly associated in HF cattle	Ciecierska <i>et al.</i> 2013, Roy <i>et al.</i> 2001
			Exon 40	Significantly associated in Murrah buffaloes	Kumar <i>et al.</i> 2017a
OLR1	5	Oxidized low density lipoprotein receptor 1	Exon 4 and Intron 4	Significantly associated in HF cattle	Soltani Ghomdavan <i>et al.</i> 2013, Wang <i>et al.</i> 2012
			3' UTR	Significantly associated in HF cattle	Schennink <i>et al.</i> 2009, Khatib <i>et al.</i> 2006
			Intron 1 and 3' UTR	Monomorphic pattern in Mehsana buffaloes	Deshpande <i>et al.</i> 2013, Shabir <i>et al.</i> 2011
ANXA9	3	Annexin-9 gene	Exon 5	Significantly associated in Spanish HF cattle	Martinez-Royo <i>et al.</i> 2009
PRLR	20	Prolactin receptor	Intron 3, 4, 5		
SCD	26	Stearoil-CoA desaturase	Exon 2, 4, 6, 9	Associated in riverine buffaloes	Javed <i>et al.</i> 2011
			Exon 3 and 5	Significantly associated in Italian HF cattle	Moioli <i>et al.</i> 2007
			Intron 3		
			Exon 5	Monomorphic pattern in Khuzestan buffaloes	Taghizadeh <i>et al.</i> 2014
DGAT1	14	Diacylglycerol- O-acyl transferase1	Exon 8	Significantly associated in HF cattle	Gautier <i>et al.</i> 2007, Grisart <i>et al.</i> 2002
Leptin	8	Leptin gene	Exon 2 and 3	Significantly associated in Murrah buffaloes	Datta <i>et al.</i> 2013
			Exon 2	Significantly associated in Murrah buffaloes	Jamuna <i>et al.</i> 2016
Ghrelin	22	Ghrelin gene	Intron 3	Significantly associated in water buffaloes	Gil <i>et al.</i> 2013
PPARGC1A	6	Peroxisome proliferator activated receptor Gamma Co-activator1 alpha	Intron 1 and 9	Significantly associated in HF cattle	Khatib <i>et al.</i> 2007, Weikard <i>et al.</i> 2005, Javed <i>et al.</i> 2011
			Intron 3 and 6	Associated in Riverine buffaloes	
			Exon 6 and 8		
PRL	23	Prolactin	Intron 1	Significantly associated in Holstein dairy cattle	He <i>et al.</i> 2006
ALG and BLG	11	Alpha and beta-Lactalbumin	Exon 1 and 2	Significantly associated with fat % and fat yield in different buffalo breeds	Vohra <i>et al.</i> 2012
		Alpha-Lactalbumin	Exon 1	Significantly associated with milk production in water buffalo	Dayal <i>et al.</i> 2006
		Beta- Lactoglobulin	Exon 1 and 4	Significantly associated with fat yield in riverine buffalo	Vohra <i>et al.</i> 2006
STAT1	2	Signal transducer and activator of transcription 1	3' UTR	Significantly associated in HF cattle	Cobanoglu <i>et al.</i> 2006
				Not-significantly associated in Murrah buffaloes	Kumar <i>et al.</i> 2015
OPN/SPP1	6	Osteopontin/ Secreted Phosphoprotein 1	Intron 4	Significantly associated with milk fat in cattle	Leonard <i>et al.</i> 2005
GHR	20	Growth hormone receptor	Intron 3	Significantly associated in Beijing Holstein cattle	Guoli <i>et al.</i> 2005

*Chr., chromosome location.

DGAT1 gene: Diacylglycerol O-acyl transferase 1 (DGAT1) is one of the main enzyme in controlling rate of triglyceride synthesis in adipocytes and plays an important role in metabolism of cellular glycerolipid. DGAT gene catalyzes the conversion of diacylglycerol and fatty acyl CoA to triacylglycerol in triglyceride synthesis. Gautier *et al.* (2007) and Grisart *et al.* (2002) reported that DGAT gene is a potential candidate gene for milk fat percentage in bovines. Grisart *et al.* (2002) and Winter *et al.* (2002) identified a variation in DGAT gene (exon 8) in *Bos taurus* cattle and found that AA converted to GC genotype resulting in substitution of amino acid 232, i.e. Lysine to Alanine and this genetic variation is associated with increased fat and protein percent as well as fat yield in milk.

FASN gene: Fatty acid synthase (FASN) gene is a complex homodimeric enzyme that controls *de-novo* biosynthesis of long-chain fatty acids and plays an important role in lipid as well as general metabolism of animals. FASN enzyme catalyzes the formation of palmitate in presence of NADPH from acetyl-coenzyme A and malonyl-coenzyme A. Chirala *et al.* (2003) reported that mammalian FASN is an important enzyme in fatty acid synthesis during adult stage as well as plays crucial role during embryonic development of individual. Mapping studies revealed the location of bovine FASN gene on 19th chromosome (Roy *et al.* 2001). Thioesterase (TE) domain has crucial role in determining the product chain length of FASN gene. Abe *et al.* (2009) reported that TE domain is a part between exons 39 to 41 of FASN gene. Vohra *et al.* (2015) reported that polymorphism is present in Exon 40 region of FASN gene in Gojri and Chhattisgarhi buffaloes. Results suggest that exon 40 region of FASN gene in Gojri and Chhattisgarhi buffaloes is highly polymorphic and sufficient genetic variability is present in this fat related gene. Kumar (2015) evaluated milk fat yield trait and found its significant association with FASN exon 40 in Murrah buffaloes. Kumar *et al.* (2016b) reported that polymorphism is present in coding region of TE domain in FASN gene with guanine to adenine transition and suggested that exon 40 region of FASN gene in Murrah buffaloes is polymorphic. This genetic variation can be used as potential candidate gene marker, which could be beneficial to animal breeders for further studies. Kumar *et al.* (2017a) reported that exon 40 of FASN gene is highly polymorphic in Murrah buffaloes and significant association of FASN gene was observed with lactation fat average, lactation total solid average and peak milk yield and this variation could be helpful to breeders for carrying out future association studies and selecting superior Murrah buffaloes for higher milk fat.

Leptin gene: Leptin is synthesized and secreted by white adipocytes of the body and travels to brain where it causes release of factors that ultimately result in increased energy expenditure, reduction of food intake as well as increased physical activity (Banks *et al.* 1996). Leptin gene is considered a potential QTL influencing different production traits including milk production in cattle (Buchanan *et al.* 2002, Soita *et al.* 2004). Dudey *et al.* (2007) reported in

their review that leptin gene is a chief candidate gene which can be used to increase production and reproduction performance of dairy as well as beef animals and genetic information related to polymorphism of leptin gene can be used efficiently in bovine breed improvement programme. Jamuna *et al.* (2016) reported that Murrah buffaloes with TC genotype of leptin gene produced more milk yield than TT and CC genotypes of leptin gene and their results revealed that C allele can be used as a potential marker for higher milk production in marker assisted selection of Murrah buffaloes.

OLR1 gene: Oxidized low-density lipoprotein receptor 1 (OLR1) plays a crucial role in degradation of oxidized low-density lipoprotein which causes damage to arterial endothelium (Imanishi *et al.* 2002). In cattle, large number of QTL affecting milk production traits had been reported in OLR1 gene including milk yield (DeKoning *et al.* 2001) and milk fat yield (Olsen *et al.* 2002). Khatib *et al.* (2006) reported significant associations of a SNP in 3' UTR region and haplotypes of OLR1 gene with fat percentage and milk fat yield in a granddaughter-design Holstein bull population and association between OLR1 haplotypes and milk production traits was further confirmed in a daughter-design study in cattle population (Khatib *et al.* 2007). Schennink *et al.* (2009) also reported a significant association between OLR1 gene polymorphism and milk fat percentage in HF cattle.

STAT1 gene: Signal transducer and activator of transcription1 (STAT1) gene is involved in the development of mammary glands and regulation of transcription of genes involved in milk protein synthesis and fat metabolism. STAT1 gene is located on chromosome number 2 (Band *et al.* 2000). In different studies, it was found that STAT1 and STAT3 are expressed at constant levels throughout lactation period, pregnancy period as well as involution period, whereas STAT4 and STAT5 are developmentally regulated (Watson 2001). Kumar *et al.* (2015) reported that 3'UTR region of STAT1 gene in riverine buffaloes is fixed or monomorphic and there were no variations at this locus and also suggested that this allele is not linked with production traits in riverine buffaloes. However, Ashwell *et al.* (2004) and Cobanoglu *et al.* (2006) reported that polymorphism in 3'UTR region in STAT1 was associated with milk fat yield and milk percentage.

Butyrophilin gene: Butyrophilin (BTN1A1) is a candidate gene related to milk yield and milk composition (fat) in dairy animals. Bovine butyrophilin gene is located on the 23rd chromosome (Ashwell *et al.* 1996). Jack and Mather (1990) reported that BTN1A1 is directly involved in secretion of fat globules at apical surface of mammary epithelial cells and is maintained throughout lactation. BTN1A1 is the most abundant protein in milk fat globule membrane and is particularly expressed in lactating mammary tissue. Ogg *et al.* (2004) also found that BTN1A1 is produced at the end of pregnancy and is maintained throughout lactation. Komisarek and Dorynek (2003) reported that BTN1A1 is a candidate gene affecting milk

yield and milk composition in bovine. Kumar *et al.* (2017b) also reported that BTN1A1 is a candidate gene affecting fat percent in dairy bovines and found that BTN1A1 gene has polymorphisms in cattle breeds but monomorphic across buffalo breeds in India.

Conclusion

Molecular markers for improving milk production as well as fat yield in bovines have proved to be beneficial to animal breeders for designing suitable breeding programme as well as to dairy producers for gaining more profit. In India, the breeding strategies in bovines should focus not only on increasing the milk yield, but also on the milk composition and its quality including fat yield. Conventional selection methodologies must be assisted by use of genetic markers for early selection as well as for more genetic gain in dairy animals. Polymorphism outlined in potential candidate genes significantly associated with milk fat percentage and fatty acid composition can be utilized as SNPs markers for selecting superior germplasm of cattle and buffaloes having quality milk production.

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