International Journal of Livestock Research, Vol. 10 (10) Oct' 2020
http://www.ijlr.org
eISSN: 2277-1964
NAAS Rating 2020 – 5.36

Review Article

Significance of Studying Candidate Gene Polymorphisms Association with Production and Reproduction Traits in Dairy Animal-A Systematic Review

Shweta Sachan*, Babu Lal Saini and Ashish Baladhare

Animal Genetics and Breeding Division, ICAR-Indian Veterinary Research Institute, Izatnagar, Uttar Pradesh, INDIA

*Corresponding Author: shwetagb24@gmail.com

How to cite this paper: Sachan, S., Saini, B., & Baladhare, A. (2020). Significance of Studying Candidate Gene Polymorphisms Association with Production and Reproduction Traits in Dairy Animal-A systematic Review. *International Journal of Livestock Research*, 10(10), 15-23. doi: http://dx.doi.org/10.5455/ijlr.20200808044513

Received : Aug 08, 2020
Accepted : Sep 04, 2020
Published : Oct 31, 2020

Abstract

Productive and reproductive performance is the key driver of the efficiency and profitability of milk production system. During the last few decades, most countries have placed varying levels of emphasis on these functional traits, hence phenotypic performance has started to improve. Recently, the underlying physiological mechanisms responsible for good or poor phenotypic productivity and fertility have started to be unraveled. The poor genetic merit for production and reproduction traits is associated with multiple artifacts in a range of tissues that are antagonistic to achieving satisfactory productive performance. The genetic value of a trait indicates the likelihood that the genes responsible for that trait will be transferred to any offspring. As other livestock traits, milk production and reproduction are influenced by many genetic loci that act directly, interact with each other, and/or interact with the environment. In recent years, molecular genetics has lead to the discovery of candidate genes with substantial effects on the traits of economic importance. Molecular genetics allows understanding the genetic structure of individuals at the genomic level and may provide the tools to make those opportunities a reality. Identification of candidate gene and use it in marker-assisted selection (MAS) serves to favorably relate alleles for quantitative characteristics with information about the individual mode of action and their interaction of genes, helping to understand the quantitative variations and their practical use in animal husbandry. In conclusion, advances in molecular technology have enabled the identification of genomic regions underlying complex phenotypic traits, and incorporation of detected quantitative trait loci into genetic evaluation provides great potential to enhance selection accuracies, hence the performance of dairy animals.

Keywords: Candidate gene, Production, Reproduction, Dairy animal, SNP, QTL

Introduction

India has the largest cattle inventory in the world (193.46 million; 20th Livestock census 2019, GOI) and ranked first in milk production (191 million metric tonnes in 2019; GOI) in the world. The rapid growth of milk production in India has been mainly due to the rise in the number of animals instead of that of improved productivity. The gradual breed deterioration generally occurs from negligence over centuries and consequent rise in the population of non-descript cows and buffaloes along with the chronic shortage of feed and fodder coupled with their nutritive values and low fertility of our dairy animals has resulted in the low productivity. There is good scope to restrict the population growth while increasing the production of milk and other products through breed improvement, balanced feeding, timely action on preventive and curative health care and post production support for enriching the value chain. The focus on genetic improvement of large ruminants should be to enhance milk production and reproductive performance, while conserving native breeds, including the draft breeds of cattle.

Till now, most genetic progress for quantitative traits in livestock, especially for dairy cows has been made by selection on phenotype or on estimated breeding values derived from phenotype, without knowledge of the number of genes that affect the trait or the effects of each gene. In this quantitative genetic approach to genetic improvement the substantial rate of improvements has been and continue to be achieved in commercial populations is clear evidence of the power of these approaches. Recently, molecular genetics has lead to the discovery of candidate genes with substantial effects on the traits of economic importance. Candidate gene strategy has been proposed by direct search for quantitative trait loci (QTL) (Tambasco *et al.*, 2003). Molecular genetics allows for the study the genetic make-up of individuals at the genomic level and may provide the tools to make those opportunities a reality, either by direct selection on genes that affect traits of interest major genes or through selection on genetic markers linked to QTL. Dekker (2004) postulated that molecular genetic approach can result in greater genetic gain than phenotypic information because 1) molecular genetic information is not affected by environmental effects and, therefore, has heritability equal to 1, 2) molecular genetic information can be available at an early age (embryo stage), thereby allowing early selection, and 3) molecular genetic information can be obtained on all selection candidates, which is especially beneficial for sex-limited traits, traits that are expensive or difficult to record, or traits that require slaughter of the animal.

Genes that lie within the confidence interval (CI) of the QTL and that have physiological relevance to the trait should be considered as primary candidates' gene. A candidate gene should have following criteria 1) the gene has a known physiological role in the phenotype of interest, 2) the gene affects the trait in question based on studies of knock-outs, mutations or transgenics in other species, 3) the gene is preferentially expressed in organs related to the quantitative trait, and 4) the gene is preferentially expressed during developmental stages related to the phenotype. Seeing the significance of the association of candidate gene polymorphisms with production and reproduction traits in cattle, information has been collected and summarized systematically in the following sub heading i.e. 1) Candidate genes for regulation of production traits in dairy animal, 2) Candidate genes for regulation of reproduction traits in dairy animal, 3) Importance of genetic polymorphisms studies in dairy animal, and 4) Tools for detection of SNPs in candidate genes related to production and fertility traits.

1. Candidate Genes for Regulation of Production Traits in Dairy Animal

The phenotypic expression of milk production traits are controlled by genes, which can or might not be transferred to the offspring. The genetic value of a trait indicates the likelihood that the genes liable for that trait are going to be transferred to any offspring. As other livestock traits, milk production is influenced by many genetic loci that act directly, interact with one another and/or interact with the environment. This makes the study of quantitative traits challenging. The establishment of the cattle genome assembly, alongside proteome and gene expression studies, has made it possible to estimate the number of genes involved in milk production, from mammogenesis to milk secretion. Around 6000-19000 genes distributed across all 29 bovine autosomes and the X-chromosome have been reported to be differentially expressed during the lactation cycle (Wickramasinghe *et al.,* 2012). Thus, the genes predicted to be involved (directly or indirectly) in the regulation of milk production, account for between 25 and 75% of all predicted cattle genes. The availability of highly informative marker maps, genome-wide association analysis, gene-based mapping and pathway analysis have resulted in the identification of several crucial regulated target genes and metabolic pathways in the mammary gland, liver and plasma that are liable for the regulation of the metabolism early in lactation.

Most genes contribute to pathways that directly affect economically important traits like milk yield and composition. Whilst regions and potential genes with effects on milk production traits are reported for nearly all bovine chromosomes, repeatedly occurring genes are located on chromosomes 27, 6, 20, and 14 (Lemay *et al.,* 2009). Only a dozen of candidate genes are consistently identified between studies and described more extensively with regards to their association with the main milk production traits. The pathways through which these genes affect milk production traits depict the variety of processes that need to be considered. Genes just like the BDNF, FTO, or IGF1 impact upon food intake and thus nutrient and energy availability (Waters *et al.,* 2012; Zielke *et al.,* 2013). Other genes like GHR, PRLR, or SPP1 affect growth, proliferation, and apoptosis of cells (Lu *et al.,* 2011a; Rahmatalla *et al.,* 2011; Zaabza *et al.,* 2018). DGAT1 and AGPAT6 are involved directly in triglyceride synthesis (Strucken *et al.,* 2010a; He *et al.,* 2011; Song *et al.,* 2019). The casein genes encode the major fraction of milk proteins (Velmala *et al.,* 1995; Pausch *et al.,* 2017; Gebreyesus *et al.,* 2019).

Table 1: Major candidate genes for production traits in dairy cattle (source: Nayeri and Stothard, 2016)

Gene		Chromosome	Trait	Discovery year
Abbreviation	**Full name**			
DIP2A	DIP2 disco-interacting protein 2 homolog A	1	Protein yield	2010
TNFSF10	Tumour necrosis factor	1	Fat yield, protein yield, fat percentage, interval from first to successful insemination (cow)	2011
SLC37A1	Solute carrier family 37 member 1	1	Milk production	2016
STAT1	Signal transducer and activator of transcription 1	2	Milk yield, fat yield, protein yield	2006
CYP27A1	Cytochrome P450, family 27, subfamily A, polypeptide 1	2	Milk yield, somatic cell score	2011
IFIH1	Interferon induced with helicase C domain 1	2	Milk yield, fat yield, fat percentage	2011
SLC40A1	Solute carrier family 40	2	Milk yield	2014
SP110	SP110 nuclear body protein	2	Fat percentage	2014
GBA	Glucosidase beta, acid	3	Protein percentage	2014
MUC1	Mucin 1, cell surface associated	3	Milk production	2016
LEP	Leptin	4	Milk protein, milk fat, lactation performance	2005
OLR1	Oxidized low density lipoprotein	5	Milk fat yield, milk fat percentage	2006
GABARAPL1	GABA type-A receptor-associated protein-like 1	5	Milk yield, fat percentage, fat production	2011
MGP	Matrix Gla protein	5	Milk yield, fat percentage	2011
MGST1	Microsomal glutathione S-transferase 1	5	Fat yield, fat percentage	2014
RPAP3	RNA polymerase II associated protein 3	5	Milk yield, protein percentage	2014
ACSS3	Acyl-CoA synthetase short-chain family member 3	5	milk fat percentage	2014
MKL1	Megakaryoblastic leukaemia (translocation) 1	5	Milk yield	2016
CSN1S2	Casein alpha-S2	6	Fat and protein percentage, milk yield	2004
CSN2	Casein beta	6	Protein yield, protein percentage, fat yield, fat percentage, milk yield)	2004
PPARGC1A	Peroxisome proliferator-activated receptor gamma, coactivator 1 alpha	6	Milk fat	2005
SPP1	Secreted phosphoprotein	6	Milk production, milk protein percentage, milk fat percentage	2005

IL8	Interleukin 8	6	Milk yield, fat yield, protein yield, somatic cell score	2007
ADAMTS3	ADAM Metallopeptidase With Thrombospondin Type 1 Motif 3	6	Milk yield and fat and protein contents	2018
CSN1S1	Casein alpha s1	6	Milk yield, fat yield, protein yield, milk fat percentage, milk protein percentage	2003
ABCG2	ATP-binding cassette, subfamily G	6	Milk yield, milk fat and protein concentration	2005
PPARGC1A	Proliferative peroxisome-activated receptor, coactivator 1	6	Milk performance	2012
CAS1A	Casein alpha s1	6	Protein percentage	2014
LARP1	La ribonucleoprotein domain family, member 1	7	Somatic cell score	2014
GRIA1	Glutamate receptor, ionotropic, AMPA1	7	Milk fat composition, milk fat percentage	2014
FBP1	Fructose 1,6 bisphosphatase 1	8	Milk performance	2012
FBP2	Fructose 1,6 bisphosphatase 2	8	Milk performance	2012
DGAT1	Diacylglycerol O-acyltransferase 1	8	Fat yield	2020
PCK2	Phosphoenolpyruvate carboxykinase 2, mitochondrial isoform	10	Milk performance	2012
GFI1B	Growth factor independent 1B transcription receptor	11	Fat percentage	2010
LGB	Lactoglobulin, beta	11	Milk protein composition, milk beta-lactoglobulin protein concentration	2003
NRXN1	Neurexin 1	11	Somatic cell score	2014
PAEP	Progestogen-associated endometrial protein	11	Milk production	2016
RNF219	Ring finger protein 219	12	Fat production	2014
SLCO1A2	Solute carrier organic anion transporter family member 1A2	12	Milk fatty acid content, milk fat percentage	2020
EP400	E1A binding protein p400	12	Protein yield	2020
ACSS2	Acyl-CoA synthetase short-chain family member 2	13	Fat yield, milk fatty acids	2011
PLK1S1	Kizuna centrosomal protein	13	Somatic cell score	2016
PCK1	Phosphoenolpyruvate carboxykinase 1, cytosolic isoform	13	Milk performance	2012
VPS28	Vacuolar protein sorting 28 homolog	14	Milk yield, protein percentage, fat yield, fat percentage	2010
MAF1	MAF1 homolog	14	Milk yield, fat percentage	2010
GPIHBP1	Glycosylphosphatidylinositol anchored high density lipoprotein-binding protein 1	14	Milk yield, protein yield, fat percentage	2010
RHPN1	Rhophilin, Rho GTPase-binding protein 1	14	Fat percentage	2010
PTK2	Protein tyrosine kinase 2	14	Fat percentage	2010
KCNK9	Potassium channel, subfamily K, member 9	14	Fat percentage	2010
COL22A1	Collagen, type XXII, alpha 1	14	Milk yield, protein yield, fat percentage	2010
CYHR1	Cysteine/histidine-rich 1	14	Milk fat composition, milk fat percentage, milk production	2014
ARHGAP39	Rho GTPase-activating protein 39	14	Milk fat composition, milk fat percentage, fat production	2014

CPSF1	Cleavage and polyadenylation specific factor 1	14	Milk fat composition, milk fat percentage	2014
GRINA	Glutamate receptor, ionotropic, N-methyl D-aspartate-associated protein 1	14	Milk fat composition, milk fat percentage	2014
FAM83H	Family with sequence similarity 83, member H	14	Milk fat composition, milk fat percentage	2014
LRRC14	Leucine-rich repeat-containing 14	14	305-day fat yield, lactose percentage	2016
FOXH1	Forkhead box H1	14	Milk production	2016
PPP1R16A	Protein phosphatase 1 regulatory subunit 16A	14	Fat production, and fat percentage	2016
SMPD5	Sphingomyelin phosphodiesterase 5	14	Fat production, and fat percentage	2016
MROH1	Maestro heat like repeat family member 1	14	Fat production, and fat percentage	2016
EIF2C2	Argonaute 2, RISC catalytic component	14	Milk yield, fat yield, protein yield	2014
TRAPPC9	Trafficking protein particle complex 9	14	Milk yield, fat yield, protein yield	2014
HEATR7A	Maestro heat like repeat family member 1	14	Fat percentage	2014
TRAPPC9	Trafficking protein particle complex 9	14	Milk yield, fat yield, protein yield	2014
DUSP10	Dual specificity protein phosphatase 10	16	Milk yield and fat and protein contents	2018
NSG1	Neuronal Vesicle Trafficking Associated 1	16	Milk production traits	2018
FGF2	Fibroblast growth factor 2	17	Milk fat, productive life	2008
GH	Growth hormone	19	Milk yield, lactation	2005
FASN	Fatty acid synthase	19	Milk fat, milk fatty acids	2007
CCL2	Chemokine	19	Milk yield, fat yield, protein yield, somatic cell score	2007
ACLY	ATP citrate lyase	19	Fatty acid biosynthesis	2009
SREBF1	Sterol regulatory element-binding transcription factor 1	19	Fat yield, milk fatty acids	2011
GHDC	GH3 domain containing	19	Milk production	2016
GHR	Growth hormone receptor	20	Milk yield and composition	2003
FYB	FYN-binding protein	20	Protein percentage	2010
RICTOR	RPTOR independent companion of MTOR, complex 2	20	Protein percentage	2010
GDNF	Glial cell-derived neurotrophic factor	20	Milk yield, fat yield, protein yield, protein and fat composition	2012
LTF	Lactotransferrin	22	Fat yield, protein yield, fat percentage, protein percentage	2006
BOLA-DRB3	Major histocompatibility complex, class II, DRB3	23	305-day milk, fat yield, protein yield	1999
PRL	Prolactin	23	Milk protein, milk yield, milk composition	2004
JARID2	Jumonji, AT-rich interactive domain 2	23	Protein yield	2014
HSPA1A	Heat shock 70 kDa protein 1A	23	Productive life, fat percent, net merit, protein percent, calving rate	2010
TRIM26	Tripartite motif-containing 26	23	Fat yield	2016
CLEC16A	C-type lectin domain family 16 member A	25	Fat yield	2016
PAM16/GLIS 2	GLIS family zinc finger 2	25	Milk yield, protein yield	2016

BTRC	Beta-transducin repeat containing	26	Fat yield	2014
PLCE1	Phospholipase C, epsilon 1	26	Protein yield	2014
SCD	Stearoyl-CoA desaturase	26	Milk fat composition, milk fat percentage	2014
SCD1	Stearoyl-CoA desaturase 1	26	Milk fatty acid content	2005
GINS4	GINS complex subunit 4	27	Fat percentage	2014
AGPAT6	1-acylglycerol-3-phosphate O-acyltransferase 6	27	Milk fatty acid content, milk fat percentage	2011
FADS1	Fatty acid desaturase 1	29	Milk omega-3 FA synthesis	2014

2. Candidate Genes for Regulation of Reproduction Traits in Dairy Animal

In dairy cattle, fertility traits are of significant economic importance. A good reproductive performance is crucial for economic as well as ethical reasons. Without reproduction there will be no animal production. The unfavorable genetic correlation with milk production has led to a decline in reproduction in dairy cattle, at least in part due to an insufficient consideration of this trait when selecting for a higher milk production (Barbat *et al.*, 2010). Many reproduction traits are difficult to handle in parameter estimation and genetic evaluation. In general, heritability's are low, usually less than 5%, mainly due to a large influence of management and environmental effects (Hansen *et al.,* 1998). Improved understanding of mechanisms that control fertility traits at the organ, cellular, and molecular level could help in developing strategies to improve and/or monitor fertility (Kiser *et al.,* 2019). Therefore, there is a great interest now in determining the relationship between fertility traits and the expression of particular genes in specific tissues. Various candidate genes regulating reproduction traits in dairy cattle have been identified (Table 2).

Table 2: Major candidate genes for reproduction traits in dairy cattle (source: Nayeri and Stothard, 2016)

Gene		**Chromosome**	**Trait**	**Discovery year**
Abbreviation	**Full name**			
TNFSF10	Tumour necrosis factor	1	Interval from first to successful insemination	2011
IGFBP2	Insulin-like growth factor-binding protein 2, 36 kDa	2	Establishment of pregnancy	2011
WNT7A	Wnt Family Member 7A	3	Female reproductive tract and maintain uterine function in adults	2018
LEP	Leptin	4	Postpartum luteal activity	2005
ATF4	Activating transcription factor 4	5	Involution pathways	2014
IGFBP7	Insulin-like growth factor-binding protein 7	6	Interval from first service to successful insemination	2011
IGFBP-5	Insulin-like growth factor-binding protein-5	6	Calving ability, mammary gland involution	2011
IRF1	Interferon regulatory factor 1	7	Involution pathways	2014
CAST	Calpastatin	7	Daughter pregnancy rate, conception rate	2006, 2013
TP53	Tumour protein p53	9	Involution, pregnancy, puberty	2007
CYP11B1	Cytochrome P450, subfamily XI B, polypeptide 1	14	Maternal calving ease	2007
CEBPD	CCAAT/enhancer-binding protein	14	Involution pathways	2014
MYC	v-myc avian myelocytomatosis viral oncogene homolog	14	Involution pathways	2014
DGAT1	Diacylglycerol O-acyltransferase 1	14	Maternal non-return rate	2002
CYP11B1	Cytochrome P450, subfamily XI B, polypeptide 1	14	Maternal calving ease, 90-day non-return rate	2010, 2007
NEU3	Sialidase 3	15	Conception rate	2013

PGLYRP1	Peptidoglycan recognition protein 1	18	Daughter calving-ease	2011
IGFL1	Insulin growth factor-like family member 1	18	Service-sire, daughter calving-ease	2011
BAIAP2	BAI1-associated protein 2	19	56-day non-return rate	2011
STAT5B	Signal transducer and activator of transcription 5B	19	Mammary development pathways, involution pathways	2014
STAT5A	Signal transducer and activator of transcription 5A	19	Fertilization rate, embryonic survival	2004, 2008
CCNB1	Cyclin B1	20	56-day non-return rate	2011
PRLR	Prolactin receptor	20	Mammary development pathways, involution pathways	2014
LIFR	Leukaemia inhibitory factor receptor alpha	20	Mammary development pathways, involution pathways	2014
OSMR	Oncostatin M receptor	20	Involution pathways	2014
HS3ST5	Heparan Sulfate-Glucosamine 3-Sulfotransferase 5	20	Reproductive seasonality	2018
PMM2	Phosphomannomutase 2	25	Daughter pregnancy rate, conception rate	2013

3. Importance of Genetic Polymorphisms Studies in Dairy Animal

In past decades, dairy breeders have used genetic evaluations to identify superior animals. Application of molecular biology tools in cattle breeding initiated the search for major genes controlling quantitative traits, but had limited success mainly because the individual gene effects tend to be small and the numbers of existing genetic markers are inadequate for estimating effects accurately (Andersson, 2001). Most breeding schemes don't account for population effects on genetic diversity, and selection is optimized for genetic response within the next generation instead of the very best long-term response (Meuwissen, 1997). This selection approach also has limited ability to enhance lowly heritable traits without adversely affecting production. Information from genetic markers that identify desirable alleles of economically important traits might be used with breeding values to guide mating decisions, leading to genetic gains over a broader range of traits. In addition, marker-assisted selection (MAS) could be used to select the most desirable phenotypes affected by non-additive gene action between loci (Jiang et al., 2019). MAS can also reduce the costs of the artificial insemination industry incurs using progeny test evaluations as the sole method for screening candidate bulls (Soller and Beckmann, 1983). Discovery and development of a large number of genetic markers are, therefore, necessary for mapping of quantitative traits in dairy animal (Matukumalli *et al.*, 2009). The problems associated with phenotypic data recording such as long time and high expense and also low cooperation of some dairymen cause to less accurate estimation of breeding values and thereafter in the selection process. Thus, collection of genotypic data by molecular methods additionally to phenotypic data is important to enhance the accuracy of selection procedure.

4. Tools for Detection of SNPs in Candidate Genes Related to Production and Fertility Traits

A genetic marker serves to favorably relate alleles for quantitative characteristics with information about the individual mode of action and their interaction of genes, helping to know the quantitative variations and their practical use in animal husbandry. Application of molecular biomarker in breeding initiated the look for major genes controlling production and reproduction traits, but had limited success. This is often mainly because the individual gene effects tend to be small and the numbers of existing genetic markers are inadequate for estimating effects accurately (Andersson, 2001). Therefore, identification of an outsized number of genetic markers is important for mapping of quantitative traits (Matukumalli *et al.*, 2009). Among the varied gene detection methods, microsatellites, amplified fragment length polymorphism (AFLPs) and restriction fragment length polymorphism (RFLPs) are one among them (Vos *et al.,* 1995). The relative high cost and limited marker density of those methods led to the utilization of a single nucleotide polymorphism (SNP) as the preferred genetic marker system. SNPs are nucleotide variations within the DNA sequence of individuals in a population and are the foremost abundant molecular marker within the genome (Vignal *et al.,* 2002). Introduction of SNPs arrays made the collection of genome-wide marker data feasible at fairly affordable costs. However, SNPs might not be a geographical representative and features a higher frequency than random SNPs. This method produces considerable ascertainment bias and intrinsically eliminates the detection of rare and population-specific variants which are a major information source for population history studies and genotype-phenotype association (DeDonato *et al.,* 2013).

The recent advances in DNA sequencing technologies have facilitated the development of more efficient and cost-effective methods that allow simultaneous discovery and genotyping of SNPs in multiple individuals. DNA markers present two possible future applications in animal selection; the combination of the best alleles of two or more breeds, and the selection of the best alleles within a breed or lineage. These methods are commonly termed as restriction site–associated DNA sequencing techniques which combine the strength of next-generation sequencing (NGS) to produce enormous numbers of DNA sequences from the ends of genomic restriction fragments with DNA barcoding for multiplexing of samples (Elshire *et al.,* 2011). Much of the work on fertility traits has been performed through use of genome-wide association studies (GWAS) to spot genetic loci associated with reproductive traits (Cole *et al.,* 2011; Minozzi *et al.,* 2013; Nayeri *et al.,* 2016).

Conclusion

There are significant and rapid advances being made in technology in the field of genetics. Because of the importance of dairy, cattle have been one of the first livestock species to benefit from these innovations, leading to the development of genomic selection. The impact of genetic selection programmes on improved dairy cow production and fertility over the past decade is supported by an abundance of scientific literature demonstrating only minor and inconsistent effects from nutritional supplementation. Importantly, well-established phenotypes associated with dairy cow production and fertility is under genetic control and may become useful in productive and reproductive genetic evaluations, if sufficient records become available. Access to large datasets of phenotypes collected from diverse cow populations with genotype information may further enhance our ability to accurately identify QTL's associated with productive and reproductive efficiency and increase the rate of genetic gain.

Acknowledgments

The authors gratefully acknowledge scientific and technical support provided by Dr. Pushpendra Kumar, Principal Scientist, ICAR-IVRI, Izatnagar, India during designing and writing of this manuscript.

Conflict of Interests

There is no conflict of interest.

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