Review

Genetic Markers Associated with Milk Production Traits in Dairy Cattle

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Abstract: Increasing milk production is one of the key concerns in animal production. Traditional breeding has gotten limited achievement in the improvement of milk production because of its moderate heritability. Milk production traits are controlled by many genes. Thus, identifying candidate genes associated with milk production traits may provide information that can be used to enhance the accuracy of animal selection for moderately heritable traits like milk production. The genomic selection can enhance the accuracy and intensity of selection and shortening the generation interval. The genetic progress of economically important traits can be doubled with the accuracy of selection and shortening of generation interval. Genome-wide association studies (GWAS) have made possible the screening of several single nucleotide polymorphisms (SNPs) in genes associated with milk production traits in dairy cattle. In addition, RNA-sequencing is another well-established tool used to identify genes associated with milk production in dairy cattle. Although it has been widely accepted that these three methods (GWAS, RNA-seq and DNA sequencing) are considered the first step in the screening of genes, however, the outcomes from GWAS, DNA-sequencing and RNA-seq still need further verification for the establishment of bonafide causal variants via genetic replication as well as functional validation. In the current review, we have highlighted genetic markers identified (2010-to date) for their associations with milk production traits in dairy cattle. The information regarding candidate genes associated with milk production traits provided in the current review could be helpful to select the potential genetic markers for the genetic improvement of milk production traits in dairy cattle.

Keywords: review; milk production; dairy cattle; RNA-seq; GWAS; DNA sequencing; polymorphism; genetic markers

1. Introduction

Milk production traits have fundamental roles in dairy development and related economy [1,2]. The bovine milk production traits such as milk yield, fat content, protein content and somatic cell score (SCS) are the essential economic traits used to measure the quality of milk [3,4]. Traditional breeding methods have achieved considerable success in many economic traits; however, milk production having moderate heritability, the gains was not fruitful with common traditional breeding [5]. Being a polygenetic trait, milk production is controlled by many genes [6,7]. Thus exploring the genetic changes underlying preferred phenotypes is the target of today's animal producers. It has been well-established that the

production of milk can be enhanced through genetic marker-assisted selection [8,9]. Various approaches such as mapping of quantitative trait loci (QTL), genome-wide association study (GWAS), RNA-sequencing, whole-genome sequencing and candidate gene analysis have been used to screen out the causal genes or their mutations associated with milk production traits [10–14]. So far, many candidate genes or polymorphisms within these genes have been identified that have a positive correlation with milk production traits in dairy cattle [1,15,16].

Through genomic selection, we can identify genetically superior animals at a very early age. The DNA-tested animals can get accurate genomically enhanced breeding values before they enter into sexual maturity. In addition, because of the heavier use of young, genetically superior males and females in genomic selection, the generation interval can be decreased. The intensity of selection can be enhanced because the breeders use genomic testing to identify a larger group of potentially superior animals. Altogether by enhancing the accuracy and intensity of selection and decreasing the generation interval, the rate of genetic progress for economically essential dairy traits can be almost doubled. Keeping in view the importance of genomic selection, the current review was designed to highlight the possible development on genetic markers associated with milk production traits in dairy cattle.

2. Materials and Methods

The data were collected through authentic sources, such as PubMed, ScienceDirect, Web of Science, SpringerLink, Scopus, and Google Scholar, using polymorphism, genetic markers, GWAS, RNA-seq, DNA-sequencing (Whole genome sequencing) and dairy cattle milk production traits as major keywords. All the published studies that have discussed the polymorphisms in genes and their association with milk production traits in dairy cattle were included in the current review. Moreover, we also included the published studies that reported the direct effect of genes on milk production traits in dairy cattle. Similarly, all the published articles in the English language and scientific citation index (SCI) peer-reviewed journals were incorporated for discussion in the current review. Furthermore, we considered articles (approximately 96%) published from 2010 onward in a present review article. Those genes from RNA-seq data associated with milk production traits and differentially expressed ($p < 0.05$, Q < 0.05) or validated through qPCR, were selected in the current review article. The present review article included all the polymorphisms in genes reported through GWAS or functional validation that were significantly associated with milk production traits in dairy cattle. Conversely, we excluded the data that was available in the form of conference papers, books, book chapters, thesis data and unpublished findings.

3. Genome-Wide Association Studies (GWAS) for Screening of Genetic Markers for Milk Production in Dairy Cattle

Genome-wide association studies have been extensively practiced to screen the polymorphism in genes associated with milk production traits in dairy cattle [17–20]. The detail of genes and their SNPs has been summarized in Table 1. Recently, Jiang et al. reported eight genes (*ACSBG2, NLK, UGDH, MAP3K1, TBC1D1, RETSAT, CENPE,* and *FCGR2B*) associated with milk production traits in 769 Chinese Holstein cows through GWAS study (Table 1) [21]. Consistently, another study documented 22 genes (*SLC37A1, ALPL, MGST1, ABCG2, MEPE, PKD2, HERC3, SEPSECS, SEL1L3, DHX15, CSN1S1, CSN1S2, CSN2, CSN3, PAEP, DGAT1, RECQL4, MROH1, BOP1, ANKH, AGPAT6* and *PICALM*) through GWAS study which were linked to milk protein in 8080 cows (2967 Montbéliarde, 2737 Normande, and 2306 Holstein) [22]. Iung et al. performed the weighted single-step genomic BLUP (WssGBLUP) method to identify genomic regions correlated with milk production traits in the Brazilian Holstein cattle population. For this purpose 75,228 phenotypic records from 5981 cows were obtained, while genotypic data of 56,256 SNPs from 1067 cows were selected for the GWAS study [23]. Finally, *ABCG2, DGAT1, MGST1, SLC37A1, LTBP1, LRRC19, PDE9A,* and *PAEP* genes were found to be link with milk production phenotypic traits in the Brazilian Holstein cattle population [23]. By using the GWAS study,

the genomic regions on BTA14 were explored for their association with milk production traits in Holstein's population (21,068 cows) selected from four different countries (Belgium, The Netherlands, Great Britain and Denmark) [24]. Through weighted single-step genomic BLUP approach, they reported several genes (*MIR2308*, *LOC104973955*, *CYHR1*, *ZNF34*, *FOXH1*, *COMMD5*, *TONSL*, *PPP1R16A*, *CPSF1*, *RPL8*, *DGAT1*, *ARHGAP39*, *GPT*, *LRRC14*, and *GML)* distributed on BTA14 that were significantly correlated with milk yield (Table 2). Many of the genes such as *TONSL*, *PPP1R16A*, *FOXH1*, *ARHGAP39*, *CYHR1* and *ARHGAP39* have also been documented by previous studies for their association with milk production traits [25–27]. Furthermore, Nayeri et al. documented that SNPs in *CPSF1*, *DGAT1*, *TONSL*, *CYHR1*, *FOXH1* and *PPP1R16A* were associated with milk yield in Canadian Holsteins [12,25]. Buitenhuis et al. [25] also showed that *GML* is significantly linked to milk fat and protein in dairy cattle. Interestingly, Poulsen et al. documented several genes such as *ALG3*, *B3GALNT2*, *LOC520336*, *PIGV*, *MAN1C1*, *ST6GALNAC6*, *GLT6D1*, *GALNT14*, *GALNT17*, *COLGALT2*, *LFNG* and *SIGLEC* by performing GWAS analysis in Danish Jersey and Holsteins [28].

By using the GWAS study, Ariyarathne et al. [29] reported key genetic markers that were associated with FP (*MGST1*, *DGAT1*, *CEBPD*, *SLC52A2*, *GPAT4*, and *ACOX3)*, PP (*CSN1S1*, *GOSR2*, *HERC6*, and *IGF1R*) and milk urea (*GMDS*, *E2F7*, *SIAH1*, *SLC24A4*, *LGMN*, and *ASS1*) of Holstein Friesian, Jersey or crossbred cows in New Zealand [29]. Similarly, Bouwman et al. documented candidate genes (*ABCG2*, *DGAT1 SCD1*, *ACLY*, *SREBF1*, *STAT5A*, *GH*, *PPARGC1A*, *ACSS2*, *AGPAT6* and *FASN*) that were significantly correlated with milk fatty acid traits in lactating Dutch Holstein Friesian at Netherlands [17]. Li et al. conducted a GWAS study for milk fatty acid traits in 784 Chinese Holstein cows and found that polymorphisms in some key genes showed a link with milk fatty acid traits [30]. Although we highlighted several genes documented through the GWAS study, however, the functional validation of these genes is highly warranted before adding them as genetic markers for milk improvement in dairy cattle breeding.

Table 1. GWAS study for screening genetic markers associated with milk production trait.

SNP (Gene)	Production Traits	Breed and Phenotypic Traits and Method Used for Association	Country	Author
rs381714237 (*FCGR2B*)	MY, PY and PP	Chinese Holstein	China	[21]
ss2137349053 (*CENPE*) rs385060942 ss2137349051 rs453960300 rs378415122	MY, FY and PY	Chinese Holstein	China	[21]
rs134985825 (*RETSAT*)	MY, FY, PP, PY	Chinese Holstein	China	[21]
rs377943075 (*ACSBG2*)	Milk FY, PP	Chinese Holstein	China	[21]
rs136639319 (*TBC1D1*)	Milk FP and PP	Chinese Holstein	China	[21]
rs379188781 (*NLK*) rs134444531	Milk PY and PP	Chinese Holstein	China	[21]
ss2137349058 (*MAP3K1*)	MY, FY and PY	Chinese Holstein	China	[21]
ss2019489562 (*UGDH*)	MY	Chinese Holstein	China	[21]
BovineHD2400007916 (*CDH2*)	Milk FP	Dual-purpose Xinjiang Brown cattle 2410 individuals with 6811 reproductive records and 5441 milk records	China	[31]
BTB-01731924 (*GABRG2*)	Milk PY	Dual-purpose Xinjiang Brown cattle	China	[31]
rs136947640 (exon10) (*FASN*)	Milk fat traits	Dual-purpose Xinjiang Brown cattle	China	[31]
rs41919985 (Exon-39) (A2266T)	Milk fat traits	Dual-purpose Xinjiang Brown cattle	China	[31]

Table 1. *Cont.*

SNP (Gene)	Production Traits	Breed and Phenotypic Traits and Method Used for Association	Country	Author
ARS-BFGL-NGS-24998 (SAA3) UA-IFASA-8605 (SAA3) BFGL-NGS-119420 (TRIB3) ARS-BFGL-NGS-69013 (SESN2) BTA-31250-no-rs (SESN2) Hapmap53714-rs29017586 (CHAC1) ARS-BFGL-NGS-5790 (NR4A1) UA-IFASA-8605 (SAA1) UA-IFASA-8605 (M-SAA3.2) BTA-68781-no-rs (HIST1H2AC) BTB-00411816 (THBS4) ARS-BFGL-NGS-85980 (FAM71A) ARS-BFGL-NGS-72191(H4) ARS-BFGL-NGS-29557 (PTHLH) ARS-BFGL-NGS-81082(ARID1B) ARS-BFGL-NGS-72191 (BoLA-DQB) ARS-BFGL-NGS-107749 (CDH16) ARS-BFGL-NGS-29490 (VEGFA) ARS-BFGL-NGS-85980 (ATF3) BTB-01766447 (RPL23A)	Milk FP, PP	U.S. Holstein cows (1654 cows, Thirty one dairy traits, including 13 production, health and reproduction traits and 18 body conformation traits) were selected for this study	U.S	[14]
ARS-BFGL-NGS-24998 (SAA1) ARS-BFGL-NGS-70836 (SAA1) ARS-BFGL-NGS-100459 (RPL23A) ARS-BFGL-NGS-24998 (M-SAA3.2) Hapmap49309-BTA-78604 (P4HA2) ARS-BFGL-NGS-70836 (ATF3)	Milk PP	U.S. Holstein cows (1654 cows, Thirty one dairy traits, including 13 production, health and reproduction traits and 18 body conformation traits) were selected for this study	U.S	[14]
ARS-BFGL-NGS-14781 (DDIT3)	Milk FP	U.S. Holstein cows	U.S	[14]
rs41569048 (PTHLH)	Milk PP	Dutch Holstein	Netherlands	[18]
rs41590827 (PTHLH)	Milk PP	Dutch Holstein, 1912 first-lactation Holstein-Friesian cows from 398 commercial herds, records of milk protein, Significance threshold used for association	Netherlands	[18]
rs41640170 (HEATR7B2)	Milk PP	Dutch Holstein	Netherlands	[18]
Hapmap51303-BTA-74377 (PTHLH)	Milk FP	Chinese Holsteins 2093 daughters as well as their 14 corresponding sires were selected to perform the current study. The numbers of daughters of the 14 sires range from 83 to 358 daughters with an average of 150. Transmission-disequilibrium test (TDT)-based single locus regression analyses and mixed model-based single locus regression analyses were performed for association analysis Milk production traits such as milk yield (MY), milk fat yield (FY), milk protein yield (PY), milk fat percentage (FP) and milk protein percentage (PP) were considered for this study	China	[32]
ARS-BFGL-BAC-2469 (HEATR7B2)	Milk FP, PP	Chinese Holsteins	China	[32]
BFGL-NGS-119420 (TRIB3)	Milk FP, PP	Canadian Holstein Data from 462 Canadian Holstein bulls were collected Single locus LD regression model was used to perform association analysis	Canada	[33]
rs29016156 (VEGFA)	Milk PP	Canadian Holstein	Canada	[33]
rs41640789 (VEGFA)	Milk FP	Canadian Holstein	Canada	[33]
rs41590827 (PTHLH)	Milk PP	Canadian Holstein	Canada	[33]
BTB-00213370 (NUB1) ARS-BFGL-NGS-71395 (SLC24A2) BTB-01052867 (SLC24A2)	Milk production traits	Gir cross Holstein (Girolando) Records of 305-day milk yield of 337 dairy cows a single-marker linear regression model was used for association	Brazil	[34]
BovineHD2900015534 (SLC22A8) BovineHD1200012381 (KLHL1) BovineHD1200012381 (KLHL1) BTB-00074258 (TBC1D5)	Milk fatty acids lactation persistence	445 Chinese Holsteins 15 milk production traits were used for this study Fixed-effect linear regression model and a mixed-effect linear model were used for association	China	[35]
BovineHD2500005573 (EEF2K) BovineHD2500005573 (EEF2K)	MY	Chinese Holsteins	China	[35]
rs109421300 (DGAT1) rs109528658 (EP400) rs42295213 (EPHA6) rs134480235 (SLCO1A2)	PP FY FP PY	Chinese Holsteins 452,920 test-day records estimated breeding values from 61,600 cows SNP regression was performed for association annalysis	China	[36]
rs211223469 (DGAT1)	FY, MY	Korean Holstein 2780 Korean Holsteins (926 bulls and 1854 cows) were used in the current study Single marker regression model for association analysis while MY, FY, PY, and SCS traits were used as milk production phenotypic traits	Korea	[37]

Table 1. *Cont.*

SNP (Gene)	Production Traits	Breed and Phenotypic Traits and Method Used for Association	Country	Author
rs41596885 (*PDE4B*), rs42314807 (*PDE4B*)	FY, MY	Korean Holstein	Korea	[37]
rs43454033 (*ANO2*)	FY, MY	Korean Holstein	Korea	[37]
ACACA rs110562092 *ADRB2* rs132839139 *AGPAT6* rs110445169 *CARD15* rs43710288 CSN1S1 rs43703010 *CSN2* rs43703011 *CSN3* rs43703015 *FABP4* rs110757796 *FGF2* rs110937773 *GHR* rs109136815 *LEP* rs11055965 *LEP* rs29004170 *LEPR* rs43349286 *LPIN1* rs136905033 *LPIN1* rs137457402 *ORL1* rs135588030 *PPARGC1A* rs44857081 *PRL* rs110684599 *PRL* rs211032652 *SCD1* rs41255693 *STAT1* rs43705173 *STAT1* rs43706906 *STAT5A* rs109578101 *STAT5A* rs137182814 *TLR2* rs43706433 *XDH* rs42890834	MFAs	1158 Italian Brown Swiss cows and The bayesian linear animal mode was used for association study were considered for current study	Italy	[38]
MIR2308, LOC104973955, CYHR1, ZNF34, FOXH1, COMMD5,TONSL, PPP1R16A, MFSD3, LRRC24, RPL8, C14H8orf33, KIFC2, RECQL4, ZNF7, ARHGAP39, GPT, LRRC14, C14H8orf82,LOC100141215, MIR2309, MIR1839, LOC101907640,LOC101908059, GRINA, LOC104968841, LOC104973958,LOC104973959, LOC104973960, ARC, SPATC1, LOC786966, LOC104973961, OPLAH, HGH1, LOC509114, JRK, PARP10, MAF1, SHARPIN, CYC1, GPAA1, MROH1, LOC523023, EXOSC4, PSCA, LY6K, GML, LY6D, LOC100848939, LOC101904969, LOC101905222, LYPD2, LOC104973965, LYNX1, LOC104973966, THEM6, SLURP1, LOC78762	Milk yield traits	In current study the data were records of 21,068 lactations on primiparous (9910) and multiparous (11,158) Holstein cows	Belgium, The Netherlands, Great Britain and Denmark	[24]
SEMA5B, AGPAT3,DGAT1, BTN1A1 SREBF1,FASN,GHR,PRLR, LIPJ, LIPK, ECHS1, ORBS1, NFKB2, CHUK,SCD1, AGPAT6	Milk fatty acids	784 Chinese and 371 Danish Holstein and 16 milk FA traits were selected for current study SNP linear regression models were used for association analysis	China	[39]
SLC37A1, MGST1, ABCG2, CSN1S1, CSN2, CSN1S2, CSN3, PAEP, DGAT1, AGPAT6, ALPL, ANKH, PICALM	Milk composition traits	Montbéliarde, Normande, Holstein 848,068 test-day milk samples from 156,660 cows in the first three lactations were collected Genotyped in 080 cows (2967 MON, 2737 NOR, and 2306 HOL)	France	[22]
SLC15A2, PEPT2, SND1, LEP, CLOCK, CASR, LRRC4, DOCK1, STAT1,STAT3, ELF5	Milk fat traits	1256 Holstein, 624 Gir, and 477 Girolando cattle Genomic BLUP Model was used for association analysis The database utilized in this study was consisted of 166,628 lactations from 94,124 cows, edited for age at calving (547 to 9095 d), calving season (dry or rainy), breed composition (determined by the proportion of Holstein breed, 1/4, 3/8, 1/2, 5/8, 3/4, or 7/8), and contemporary group (determined by herd-year of calving).	Brazil	[40]
rs443751026-*GPATCH4* upstream rs210886822 *MGST1* intron rs209288972 *MGST1* upstream rs208317364 *DGAT1* intron rs133931291 *HSF1* intron *LGALS12* upstream rs383292923 *ANK1* intron rs208624037 *GPAT4* intron rs467849681 *ARHGEF28* intron	Milk fat	Montbéliarde, Normande, Holstein 15 traits (5 linked with milk production, 2 with udder health, and 8 with udder morphology) in Montbéliarde (MON), Normande (NOR), and Holstein (HOL) cattle were selected. The phenotypic data was collected from 2515 MON, 2203 NOR, and 6321 HOL bulls and verified in 23,926 MON, 9400 NOR, and 51,977 HOL cows Illumina Bovine SNP50 BeadChip (50K; Illumina Inc., San Diego, CA, USA) was used for genotyping	France	[20]

Table 1. *Cont.*

SNP (Gene)	Production Traits	Breed and Phenotypic Traits and Method Used for Association	Country	Author
BTB-01603522-*ACSL1*				
BTB-01926888-*ACSL1*				
BTA-111275-no-rs-*PRKG1*				
BTB-01077939-*PRKG1*				
Hapmap26394-BTA-136497-*CNTN3*				
Hapmap26394-BTA-136497-*CNTN3*				
ARS-BFGL-NGS-101978-*HTR1B*				
BTA-12468-no-rs-*IGF1R*				
BTA-12468-no-rs-*IGF1R*				
BTA-76414-no-rs-*IGF1R*				
BTA-76414-no-rs-*IGF1R*				
ARS-BFGL-NGS-40159-*PLIN1*				
Hapmap49848-BTA-106779-*CPM*				
BTB-01556197-*HTR1B*				
BTB-01556197-*HTR1B*				
ARS-BFGL-BAC-35400-*FAM46A*				
ARS-BFGL-BAC-35400-*FAM46A*				
ARS-BFGL-NGS-61979-*UBE3D*				
ARS-BFGL-NGS-61979-*UBE3D*				
ARS-BFGL-NGS-34500-*ACACA*				
ARS-BFGL-NGS-39328-*FASN*				
Hapmap58547-rs29023020-*PRL*				
ARS-BFGL-NGS-111111-*AGPAT3*				
ARS-BFGL-NGS-109493-*AGPAT3*				
BTA-56389-no-rs-*AGPAT3*				
ARS-BFGL-NGS-45691-*FABP3*				
ARS-BFGL-NGS-118924-*FABP3*				
RS-BFGL-NGS-4939-*DGAT1*				
ARS-BFGL-NGS-118998-*GHR*				
BTB-01373917-*STAT1*				
ARS-BFGL-NGS-33744-*STAT1*				
BTB-00965197-*NRG1*				
ARS-BFGL-NGS-107403-*NFKB2*		Chinese Holstein		
ARS-BFGL-NGS-23064-*SCD1*		Phenotypic data for 22 milk fatty acids in 784 Chinese Holstein		
ARS-BFGL-NGS-77668-*SCD1*	Milk fatty acid traits	cows was used	China	[30]
BTB-00930925-*SCD1*		Significance threshold was considered		
ARS-BFGL-NGS-39397-*SCD1*				
BTB-00930720-*SCD1*				
Hapmap31825-BTA-158647-*SCD1*				
Hapmap33073-BTA-162864-*SCD1*				
BTB-00931481-*SCD1*				
ARS-BFGL-NGS-110077-*SCD1*				
ARS-BFGL-NGS-108305-*SCD1*				
BTB-00931586-*SCD1*				
ARS-BFGL-NGS-114149-*SCD1*				
ARS-BFGL-NGS-116481-*SCD1*				
Hapmap24832-BTA-138805-*SCD1*				
ARS-BFGL-NGS-6259-*SCD1*				
BTB-00932332-*SCD1*				
Hapmap46411-BTA-15820-*CHUK*				
BTA-61921-no-rs-*LIPJ*				
ARS-BFGL-NGS-21794-*LIPK*				
ARS-BFGL-NGS-29299-*SORBS1*				
Hapmap41595-BTA-60800-*SORBS1*				
Hapmap58930-rs29010490-*SORBS1*				
Hapmap28763-BTA-162328-*ECHS1*				
Hapmap28763-BTA-162328-*ECHS1*				
ARS-BFGL-NGS-116897-*OLR1*				
Hapmap26001-BTC-038813-*PPARGC1A*				
Hapmap31284-BTC-039204-*PPARGC1A*				
Hapmap49746-BTA-76106- *PPARGC1A*				
ARS-BFGL-NGS-12970-*FADS1*				
ARS-BFGL-NGS-1448-*AGPAT6*				
ARS-BFGL-NGS-85864- *CYP26A1*				
BTB-00927439- *CYP2C19*				
BTB-01423653-*PRLR*				
BTB-01423676-*PRLR*				
Hapmap30570-BTA-152778-*PRLR*				

MY: milk yield; FY: fat yield; FP: fat percentage; PY: protein yield; PP: protein percentage; MFAs: Milk fatty acids. *Eukaryotic elongation factor 2 kinase (EEF2K); kelch like family member 1 (KLHL1); EPH receptor A6 (EPHA6); solute carrier organic anion transporter family member 1A2 (SLCO1A2); diacylglycerol O-acyltransferase 1 (DGAT1); E1A binding protein p400 (EP400); phosphodiesterase 4B (PDE4B), and anoctamin 2 (ANO2).*

4. Transcriptomic Analysis for Screening of Genetic Markers Associated with Milk Production

RNA-sequencing has been a newly merged tool for screening genetic markers associated with milk production [2,10]. Besides genetic data, the gene expression profile also plays a vital role in exploring the underlying mechanism for complex traits such as milk

production in dairy cattle. Constantly, Cui et al. performed the transcriptomic profiling of the bovine mammary gland of four lactating Chinese Holstein cows with high and low phenotypic milk protein and fat percentage values. They reported some promising candidate genes (*TRIB3, SAA1, M-SAA3.2, SAA3, VEGFA, PTHLH, HSPD1, KRT24,* and *RPL23A*) that were significantly correlated with milk protein and milk fat percentage [10]. Bagnato et al. also reported the significant association of *HSPD1* and *KRT24* genes with milk yield and protein percentage in Brown Swiss dairy cattle [41]. Furthermore, Khan et al. by using RNA-seq analysis reported the number of genes (*DGAT2, ALOX5, AGPAT4, GPAT3, GGH, ALDOA, TKT, SLC11A1* and *LAP3)* in response to folic acid treatment that were associated with milk protein, milk yield and milk fat in dairy cattle [2]. Consistently, Ouattara et al. reported that vitamin B9 and B12 combine supplementation regulated key genes that were associated with milk production traits. Furthermore, the candidate genes (*MYOM1, HP, CDK5R1, MEP1B, DLK1, PPP1R3B, GSTA5, HERC6, LOXL4, SAA3, FUT5, PYCR1* and *CACNA2D1)* they documented were linked to milk protein and milk fat traits [42]. The genes associated with milk production traits screened out through RNA-seq by different studies have been summarized in Table 2.

Table 2. Genes identified through the RNA-seq method.

Genes	Production Traits	Breed	Country	Author
LRRC73, GPX3, APOA4, HP, MFSD2, CDC42EP5, SLC13A5, SMCT1, PAQR9, SFRP2, ISG15, IFIT1, RSAD2, APOA4, MX1, MX2, USP18, LOC100298356, HERC6, ISG12(B), TLH29, RSAD2, IFIT1, FKBP5, FKBP,RXRG, ITGAD, LYZ2,HBB APOC2, ACADVL, PPP1R3B, GALE, PKLR, ANGPTL4, CDKN1A, ODC1, LPIN1, DUSP1, LMNA, APOA1, ABCG8, Kb, SAA1, PC, SDS, GADD45B, IGF-1R, CYP7A1,GK, SGLT1, FBP2	MY, FY, PY, FP	Holstein	China	[43]
C4BPA, SLC25A38,BMX, EIF4G3, ZC3H14, FCAMR, DNER, SAA3, HEATR7B2, TRIB3, SESN2, CHAC1, NR4A1, SAA1, ATF3, RPL23A, CDH16, VEGFA, BoLA-DQB, ARID1B, PTHLH, H4, FAM71A, THBS4, DDIT3, M-SAA3.2, HIST1H2AC, P4HA2, HSPD1, KRT24, CDKN1A	FP, PP	Holstein	China	[10]
GGT5, CYP2J2, ALOX12, MIF, LPL, CPT1A	MFAs	Holstein	China	[44]
CSN2, CSN1S1, LGB, CSN3, CSN1S2, LALBA, GLYCAM1, COX1, FASN, CLU, COX3, MT-CYB, XDH, MFGE8, EEF1A1, GPAM, ATP6, MT-ND3, ND1, MT-ND4, NADH, SPP1, SERPINA1, CNTFR, ERBB2, NEDD4L, ANG, GALE, HSPA8, LPAR6, WAP, NARS, MARS, GARS, CDO1,GATM, INSR, IGF1R, IGFBP3, CRIM1, IGFBP3	Milk protein traits	Holstein	China	[45]
SLC22A1, MAPK9, PPARGC1A, FOXO1, SOCS1, SOCS2, CREB1, HNF4A, HNF4G, GADD45A, DUSP1, PDGF, SYBU, DDIT4, BAMBI, MTHFR, SLC27A2, PCK1, CPT2, SIRT3, CYP4A11, PLCB2	Milk protein and fat	Holstein	China	[46]
SLC27A6, ACADM, ACADs, IDH1, FABP4, CACYBP, KLHL9, UBE2B, RPS, SLC7A8	Milk protein	Holstein	China	[47]
LALBA, LGB, CSN1S1, CSN1S2, CSN2, CSN3, GK,GPD1, DHCR24, COQ2, AGPAT6, GPAM, LPIN1, BTN1A1, XDH, PLIN2, SCD5,DGAT1, FADS1, FABP3, SLC22A16, ACSS1, ACSS2, ADIPOQ, HADHB, SLC1A2, SLC1A5, SLC7A4, SLC7A8, SLC38A3, SARS, PAH, ASNS, RPL,ELOVL, EIF4EBP1, INSIG1	Milk protein and fat	Holstein	China	[47]
LAP3, ASS1, CYP2J2, ATP6AP1, SDS, DGAT2, AGPAT4, GPAT3, ALOX5, HSD17B12, HACD4, PPT2, ELOVL6, EPHX1, LPL, GUK1, XDH	Milk fat and protein yield	Holstein	China	[2]
GPC5,TECTB,IARS2,GUK1,HS3ST5, STMN4,CALB1,LALBA,GLYCAM1 GP2, LPL, SLC34A2, TUBA1C, CSN1S1, CSN2, PTHLH, BDA20, BDA20, ALOX15, STATH, BOLA-DQA1, TTC36, PAEP, SPINK4, BTN1A1, TMOD4, SCD, MYBPC1, ASB11, SLC38A3	MY	Holstein	China	[48]
IRF6, AGPAT6, STAT5A, XDH, B4GALT1,BCL2L11, PRLR, ALOX5, PRKAA1, NCF1, AGPAT6,STAT5A, CRYL1, GPAM, ALOX12, PGHS-2, CPT1B, SLC27A1, PRKAR2B, FADS6, PPARD, ACACA, PTGES, EHHADH	Milk fat synthesis	Holstein	China	[49]

MY: milk yield; FY: fat yield; FP: fat percentage; PY: protein yield; PP: protein percentage; MFAs: Milk fatty acids.

5. Whole-Genome Sequencing for Screening of Genetic Marker Associated with Milk Production in Cattle

Whole-genome sequencing is one of the next-generation sequencing methods utilized to identify a large number of SNPs more quickly and inexpensively [50]. The DNA-seq

method has been widely excised in livestock genomics to identify the genetic markers associated with milk production traits [51,52]. To perform whole-genome sequencing, the data composed of about 254 k milk, fat, and protein test-day records were collected from 7522 Holstein cows calved from 2006–2016 on two dairy farms in the state of Florida [53]. They reported several genes (*CDKN1B*, *DUSP16*, *HSF1*, *EEF1D*, *VPS28*, *TONSL*, *PEX16*, *MAPK8IP1*, *CREB3L1* and *CRY2*) on BTA5, BTA14 and BTA15 that were significantly associated with milk production in traits in dairy cattle. Interestingly, the reported genes in this study are involved in the inositol phosphate mediated signaling pathway, insulin receptor signaling pathway, JNK cascade, stress-activated MAPK cascade, *and* glutamine metabolic process. These pathways play a major role in maintaining milk production even under stressful condition to regulate the antioxidant system [53]. Similarly, Nanaei et al. performed DNA sequencing for screening genetic makers associated with milk production traits by using the Illumina whole genomes of 21 cattle individuals, including 3 indigenous African breeds (Ankole *n* = 4, Kenana *n* = 4 and N'Daman = 6), and two commercial breeds (Polish Holstein-Friesian *n* = 3 and Hereford *n* = 4). Importantly, they documented some key genes (*IGFBP2*, *B4GALT1*, *RORA*, *LPIN1*, *ATP2B*, *CSN3*, *NME1*, *ACACA*, *PDE3A*, *XP-CLR*, *KCNIP4*, *GHR*, *NF2*, *ABCC9*, *CD44*, *MACF1*, *IL15*) involved in the regulation of biological function processes such as phosphorus metabolic process, phosphate-containing compound, metabolic process, phosphorylation, protein phosphorylation" and metal ion transport that were significantly related with milk production traits [54]. Recently a study selected 45 blood samples from two-year-old animals and DNA-sequencing was carried to identify genetic markers associated with milk production traits [55]. Interestingly they found nine genes (*ADCY5*, *CACNA1A*, *CREB1*, *INHBA*, *INHBB*, *PIK3R1*, *PLCB1*, *PRKCE*, and *SMAD2)* distributed in the ionotropic glutamate receptor pathway, the endothelin signaling pathway, and the gonadotropin-releasing hormone receptor pathway, which are involved in the hormonal regulation of lactation [55]. Whole-genome sequencing for data obtained from 4280 progeny tested Nordic Red Cattle bulls was performed to identify the genetic markers for milk production [56]. In addition, the genes related to milk production traits including *DGAT1*, *HSF1*, *TRIM26*, *CLEC16A*, *NEURL1* (Fat yield), *MKL1*, *CPSF1*, *ADCK5*, *LAX1*, *GHR* (milk yield), *DGAT1*, *HSF1*, *UNKL*, *PAM16*, *GLIS2* (protein yield) were documented in Nordic Red Cattle [56].

6. DNA Polymorphisms and Their Association with Milk Production Traits in Dairy Cattle

The correlation of DNA polymorphisms with milk production in dairy cattle has been studied for several genes, including *SCD*, *prolactin*, *DGAT1*, *leptin*, *GHR*, *CSN1S1*, *ABCG2*, *GH* etc. In Table 3, we have summarized all the major DNA polymorphisms in genes and their association with milk production traits in dairy cattle.

Stearoyl-CoA desaturase 1 (SCD1) located on chromosome 26 has been widely studied for its association with milk production traits in dairy cattle [57–62]. Taniguchi et al. studied the polymorphisms of *SCD* in Holstein-Friesian, Jersey, Brown Swiss, and Japanese black cattle breeds and found their association with milk fat composition [60]. Similarly, Kgwatala et al. documented the SNP at 3-UTR of *SCD* and their link with milk fatty acids in Canadian Holstein and Jersey breeds [62]. Consequently, Macciotta et al. reported that the Italian Holsteins with VV genotypes produced more milk and protein than those with AA genotypes. In contrast it has been reported that cows with AA genotypes were producing more milk fat [61]. Furthermore, they highlighted that because of the involvement of *SCD* gene in energetic pathways, it might be the reason for their association with milk production traits such as milk, yield, and protein [62]. Mele et al. [59] studied the genotypic effect of *SCD* on milk fatty acids in 297 Italian Holstein Friesian cows. The genotypes in *SCD* were confirmed through the single-strand conformation polymorphism method. Interestingly, they found that cows having AA genotypes producing more milk fat compared to VV genotypes cows [60]. The above results were also verified by a recent study who found that heterozygous genotypes Chinese Holsteins were producing more milk than the cows of homozygous genotypes [63]. Similarly, Kesek-Wozniak et al. reported that heterozygous

genotypes Polish Holstein-Friesian cows produced more milk fatty acids in milk compared to VV and AA genotypes cows [64].

Alim et al. [63] reported several SNPs in the *SCD* gene and their association with milk production traits in Chinese Holsteins. They documented that polymorphism g.10329C/T at exon 5 changed the amino acid alanine to valine. In addition, it was noticed that the two SNPs (g.6926A/G and g.8646A/G) at intron 3 and three polymorphisms (g.10153A/G, g.10213T/C and g.10329C/T) at exon 5 in *SCD* were significantly associated with milk fat, milk yield, protein yield and protein (%) in Chinese Holsteins [63]. Recently, it has been documented that A293V (c.878C/T) mutation in *SCD* changed the amino acid alanine to valine and is associated with milk fatty acid in Polish Holstein-Friesian cows [64]. Constantly, Bouwman et al. reported that the A allele of SNP in *SCD* was associated with higher milk fatty acids [17], while other studies found the less effect of V allele on milk fats in White Fulani and Borgou cattle breeds [65,66].

The polymorphism (*DGAT1* K232A) in *DGAT1* has been widely studied for its association with milk production traits particularly milk fatty acids in dairy cattle (Table 2) [64,66,67]. In addition, it has been documented that K allele is linked to high milk fat yield, fat content, and protein content and lower milk production protein and lactose yield [68,69]. While other studies reported that cows with AA genotypes have higher milk yield and lactose yield and low milk fat and protein contents [70–72]. Based on the above findings, it can be concluded that the *DGAT1* K232A can be a target as a useful genetic marker for milk production improvement in dairy cattle.

Raschia et al. conducted a study in Argentina and reported several SNPs in selected candidate genes for their association with production traits in 20 Holstein and 5 Jersey cows. Furthermore they documented that the genes including *ARL4A* (rs43375517), *SCD1* (rs41255693), *GH* (rs109191047; rs137651874), leptin (rs29004488), OPN (rs132812135), *PRLR* (rs135164815) and *LTF* (rs43706485) were associated with milk production traits [73]. Moreover, the SNPs (SNP1; G43737229T, SNP2; G43737229T, SNP3; G43761121A, SNP4; G43761121A, SNP5; G43761121A, SNP6) in *breast cancer 1 (BRCA1)* gene were significantly associated with milk yield in Karan Fries (*Bos taurus* × *Bos indicus*) cows [74]. However the stage of lactation (lactation 1, 2 and 3) and genotypes (GG, TT, TG) of cows were the key factors that affected the effect of SNPs on milk yield in Karan Fries cows [74].

Fatty acid desaturase 2 (FADS2) is another promising candidate gene that influences milk fatty acid traits and is located on bovine chromosome 29, with 16 exons encoding 359 amino acid chains [75]. The polymorphism in the *FADS2* gene has been widely studied for its association with milk fatty acids (MFAs) in dairy cattle [43,76,77]. Based on published data, it can be recommended that the *FADS2* can be a useful candidate marker for milk fat traits improvement in dairy cattle. The detail of *FADS2* gene and their polymorphisms has been given in Table 3.

Ahmed et al. documented few milk protein genes (*CSN1S1*, *CSN2*, *CSN1S2*, *CSN3*, *LALBA*, and *LGB*) that were linked to increase milk protein traits in Sudanese Butana cattle [78]. Consistently, *CSN1S1*, *CSN2CSN2*, *CSN2*, *CSN1S2*, *LALBA* genes have been studied for their association with milk production traits in other *Bos indicus* breeds such as Sarabi, Sistani, Golpayegani and Gir in Iran and Brazil, respectively [79,80]. Moreover, Miluchová et al. proved experimentally that the CSN3 gene was significantly associated with milk production traits in the Slovakian Holstein population [81].

Haruna et al. had documented that the myostatin gene was significantly associated with increasing the amount of milk unsaturated fatty acid and decreasing the amount of saturated fatty acid in New Zealand Holstein-Friesian cross Jersey-Cross Cows. Moreover, they reported that cows with AD genotypes were linked to decreased saturated fatty acid while cows with AA genotypes correlated with increased milk unsaturated fatty acid [82]. Consequently, it has been documented that *fatty acid-binding proteins (FABPs)* is significantly associated with milk fatty acids synthesis in Holstein-Friesian × Jersey (HF × J) dairy cows [83].

The *glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein1 (GPI-HBP1)* is a key gene that has been studied for its association with milk fat (%) and milk protein yield [32,84]. Consistently, another study had reported that *GPIHBP1* was significantly correlated with milk fat traits in Chinese Holsteins [85]. They demonstrated that when the expression of *GPIHBP1* was decreased, which decreased the LPL binding ability to *GPIHBP1* and alternatively, the process of lipolysis was inhibited in mammary epithelial cells, resulting in increased fat in milk [85]. Moreover, Dong et al. [86] illustrated that the decrease of the expression of *GPIHBP1*, result in an increase in milk protein genes (*CSN1S1*, *CSN1S2*, *CSN2*, and *CSN3*, *lactoferrin*) which were associated with the regulation of milk protein biosynthesis [86].

Long-chain acyl-CoA synthetase 1 (ACSL1) is located on chromosome 27 of cattle (Bos Taurus), having 20 exons, 19 introns with 64,883 bp length [87]. The SNPs detected in the *ACSL1* gene were genotyped in 992 Chinese Holstein cows and documented the significant association of these SNPs with milk production traits [87]. Consistently a study also documented the up-regulation of sic genes (*ACACA*, *GPAM*, *ACSL1*, *FASN*, *LPIN1* and *ACSL6*) in dairy cattle during lactation [88]. Twenty candidate genes associated with milk fatty acid traits in Chinese Holstein cows were identified in a previous study, and *ACSL1* was one of them [30]. Furthermore, a study had documented that mutation in the *ACSL1* gene plays a key role in the milk fat enhancement of Yak [89]. Fan et al. experimentally proved that the expression (increase and decrease) of *ASCL4* was significantly associated with milk fat synthesis in bovine mammary epithelial cells [90]. The interaction of *ASCL4* was reported with *ASCL1*, *FADS2*, *FASN*, *PPARD*, *CPT1A*, *FABP3* and *ELOVL6* which are key genes associated with milk production traits. Based on the above findings, we can conclude that *ASCL1* can be considered a key regulator of milk fat synthesis.

Acylglycerol-3-phosphate O-acyltransferase 3 (AGPAT3), located on Bos taurus autosome 1 (BTA1) having eight exons encoding 376 amino acid chains, is a crucial acyltransferase that is involved in triglyceride (TG) and phospholipid biosynthesis [91]. *AGPAT3* has been identified through GWAS studies as a positional candidate gene affecting milk fatty acids in dairy cattle [30,91,92]. A study by using GWAS study documented the *AGPAT3* and was found to be significantly linked with milk fatty acid traits in Chinese and Danish Holstein populations [39]. Recently, a study detected a SNP1 (g.12264 C > T) at promoter region, SNP2 (g.18852 C > T) in exon 5 and other six SNPs (g.18658 G > A, g.20046 G > A, g.23034 C > A, g.28332 C > T, g.28484 C > T, and g.28731 A > G) on intronic regions of *AGPAT3* in dairy cattle [93]. All the SNPs reported by Sun et al. showed significant association with at least one phenotypic trait of milk production. Similarly, Shi et al. reported 17 SNPs in *AGPAT3* that were associated with milk fatty acid traits in Chinese Holstein cows [94]. Littlejohn et al. also documented several SNPs of *AGPAT3* in Holstein-Friesian × Jersey crossbreed that were associated with milk fat synthesis [95]. The detail of SNPs in *AGPAT3* has been given in Table 3.

Prolactin is another key gene having an important role in lactation initiation and maintenance in mammals [96]. Several polymorphisms within prolactin have been identified which were significantly associated with milk production traits in dairy cattle [96,97]. Poglo et al. identified *BACH2*, *E2F3* and *KDM5A* as key genes that are involved in the regulation of milk fat synthesis in the mammary gland of dairy cattle [98].

Table 3. The variations in genes and their association with milk production traits in dairy cattle.

Gene (Location)	Polymorphism (Location)	Change in Amino Acid Sequence	Production Trait	Breed	Country	Author
SERPINA1 (BTA21)	rs208607693 (5- flanking region) rs210222822 (Exon-2)		MY, FY, PY, PP	Chinese Holstein	China	[99]
SERPINA1 (BTA21)	rs41257068 (Exon-2) rs207601878 (Intron-3)		MY, FY, PY, PP, FP	Chinese Holstein	China	[99]
SCD (BTA21)	c.878C/T (Exon5)	p.A293V	MFAs	Holstein Friesian × Jersey dairy cows	Newzealand	[100]
SCD (BTA21)	c.1783A/G (3-UTR)		MF	Holstein Friesian × Jersey dairy cows	Newzealand	[100]
SCD	g.10329C > T	Alanine to valine	MY, FY, PY, PP	Chinese Holstein	China	[101]
	g.10153G > A					
	g.10213T > C					
SCD	g.10329C > T	Alanine to valine	MFA	Canadian Jersey cows	Canada	[62]
SCD	g.10329C > T	Alanine to valine	FY, PY, MY	Holstein cows	Belgium	[102]
SCD	A293V SNP		MFAs	Polish Holstein-Friesian	Poland	[64]
SCD	A293V SNP		MFAs	Italian Holsteins	Italy	[59]
CD4 (BTA5)	g.13598C > T		MY, FY, PY	Chinese Holstein	China	[103]
STAT5B (BTA19)	g.31562T > C; Exon 16		MY, PY	Chinese Holstein	China	[103]
DDIT3 (BTA5)	g.56283814C > T;5-flanking region g.56284880C > T;5-flanking region		FP, FY, PP	Chinese Holstein	China	[15]
	c.*21A > G (5-UTR)		MY, FY, PY		China	[15]
RPL23A (BTA19)	g.20702088A > G 5-flanking region g.20702122C > G 5-flanking region g.20702782_83insG 5-flanking region		MY, FY, PY	Chinese Holstein	China	[15]
SESN2 (BTA19)	g.125716884A > G, 5-flanking region g.125714860_125714872del, 5-flanking region g.125714806delinsCCCC, 5-flanking region g.125714850A > G, 5-flanking region g.125716686A > G, 5-flanking region		MY, FY, PY	Chinese Holstein	China	[15]
NR4A1 (BTA5)	g.27994068A > G, 5-flanking region g.27993737A > G, 5-flanking region g.27992897C > T, 5-flanking region c.*138A > G (5-UTR)		MY, FY and PY	Chinese Holstein	China	[15]
PTK2 (BTA14)	g.4061098T > G (Exon5)	p.Ile981Met	MY, PY and FP	Chinese Holstein	China	[104]
	g. 3895208T > G (Intron2)		MY, PY and FP			
	g. 4059863 A > C (Intron13)		MY, FY, PY and FP			
	g.3968605A > G (Intron6)		MY, PY and FP			
	g.7012367T > C (Intron16)		MY, FP and PP			
UGDH (BTA6)	rs61000233G/A (Exon1) rs60966191A/T (Exon12)		MY	Chinese Holstein	China	[105]
SAA1 (BTA11)	g.-1788C > T (Promoter) g.-963C > A (Promoter) g.-781 A > G (Promoter)		PY, MY	Chinese Holstein	China	[106]
	c. + 2510A > G (EXON3)	Gly48Asp	MY, FP and PY			
	c. + 2535C > T(EXON3)	R56R	PY, MY			
	c. + 2565G > A (EXON3)	P66P	PY, MY			
SAA2 (BTA29)	c.-22G > A (Promoter) c.17G > C (Promoter) c.114G > A (Promoter)		MY, FY and PY	Chinese Holstein	China	[107]
ACACB (BTA17)	g.66218726T > C (Promoter) g.66218117G > A(Promoter)		milk production traits	Chinese Holstein	China	[108]

Table 3. *Cont.*

Gene (Location)	Polymorphism (Location)	Change in Amino Acid Sequence	Production Trait	Breed	Country	Author
ERBB2 (BTA19)	g.22400A > G (Intron-23) g.22346A > T (Intron-23) g.16431C > G (Intron-14) g.19414A > G (Intron-14) g.11680C > T (Intron-8) g.10727A > G (Intron-7) g.23650T > C (Intron-26) g.22268T > C (Exon 23) g.20982del (Intron-19)		Milk PP	Chinese Holstein	China	[109]
ERBB2	g.873T > C (5-flanking region) g.21561A > G (Exon-21)		MY, FY, FP, PY, PP	Chinese Holstein	China	[109]
HSPA8 (BTA15)	rs132976221 g.4218T > G (Intron-3)		MY, PY, FY	Chinese Holstein	China	[109]
HSPA8	rs136632043 g.4218T > G-exon9		MY, PY, FY	Chinese Holstein	China	[109]
ECHS1 (BTA6)	g.25858322C > T-exon 3	Leucine-phenylalanine	MFAs	Chinese Holstein	China	[110]
ECHS1	g.25857784C > T(exon 2)		MFA	Chinese Holstein	China	[110]
FADS2 (BTA29)	c. 908 C > T (Exon 7)	294Ala > Val	MY, PY, FY, FP	Chinese Holstein	China	[111]
FADS2	c.1571 G > A (3-UTR)		MY	Chinese Holstein	China	[111]
FADS2	c.1571G > A (3-UTR)		MFA	Chinese Holstein	China	[75]
FADS2	rs209202414 G > A		MFA	HS and Jersey	Romania and Poland	[77]
FADS2	rs211580559 G > A(exon 7)	(294 Ala > Val)	MFA			[76]
	rs42187261 G > A (exon 8)		MFA			[76]
	rs109772589 G > A (3-UTR) rs136261927 G > A (3-UTR) rs109772589 G > A (3-UTR)		MFA	Canadian Holstein	Canada	[76]
THRSP (BTA29)	rs42714482 (exon 7)	Ala51Val	MFA	Jersey and Polish Holstein	Poland	[112]
SCD 1 (BTA26)	rs41912290 G > A (Exon16)	Leu/Pro	MFA	Holstein	US	[113]
	rs41255691 (Exon 5)			Holstein	US	[113]
SCD5 (BTA6)	ss252452201 (exon 3) ss252452202(exon 3) ss252452203(exon 3) rs43687655 (exon 4)		MFA	Holstein	US	[113]
INSIG1 (BTA4)	ss252452218 (Exon 1) ss252452220 (exon4) ss252452222 (exon5)	Ser/Gly Leu/Phe	MFA	Holstein	US	[113]
INSIG2(BTA4)	ss252452227 (5′UTR) ss252452228 (5′UTR) ss252452229 (5′UTR)		MFA	Holstein	US	[113]
MBTPS1 (BTA18)	ss252452238 (Exon 1)		MFA	Holstein	US	[113]
MBTPS2 (BTA18)	ss252452240 (5′UTR)		MFA	Holstein	US	[113]
SCAP (BTA12)	ss252452209 (5′UTR) ss252452210 (5′UTR) ss252452212 (exon 3) ss252452215 (exon 7) ss252452217 (exon 7) rs41255691 (exon5)		MFA	Holstein	US	[113]
SCAP (BTA12)	ss252452215 (exon 7)	Pro/Ser	MFA	Holstein	US	[113]
MAP4K4 (BTA11)	c.2061T > G (exon 18)		PP, MY	Chinese Holstein	China	[114]
IGF2R	g.72479 G > A (exon 24)		MY, PY, LC	Polish Holstein	Poland	[115]
Sirtuins (BTA28)	g.-274C > G (Promoter)		MY, FY, FP, LL	Chinese Red Steppe Agerolese, Qinchuan Nanyang, Jiaxian, Luxi	Italy	[116]
SCD	*SCD1*-A293V	A293V	MFA	Holstein	Netherlands	[65]
FASN (BTA19)	rs41919999 (Intron 12) rs41919992 (Exon-27) rs133498277 (Intron 28) rs41919984 (Exon 37) rs41919986 (Exon-42)		MCFAs	Chinese Holstein	China	[117]

Table 3. *Cont.*

Gene (Location)	Polymorphism (Location)	Change in Amino Acid Sequence	Production Trait	Breed	Country	Author
FASN	rs41919985 (Exon-39)	alanine 2266threonine	MCFAs	Chinese Holstein	China	[117]
PPARGC1A (BTA6)	rs109579682-Intron-9		MCFAs	Chinese Holstein	China	[117]
ABCG2 (BTA6)	rs137757790-Intron-7		MCFAs	Chinese Holstein	China	[117]
IGF1 (BTA5)	rs109763947-5′-UTR		MCFAs	Chinese Holstein	China	[117]
ABCG2	ABCG2-Y581S		MY, FP, PP	Iranian Holstein	Iran	[118]
LEPR (BTA3)	LEPR-T945M		MY, FP, PP	Iranian Holstein	Iran	[118]
SCD1	SCD1-A293V		MY, FP, PP	Iranian Holstein	Iran	[118]
DGAT1 (BTA14)	DGAT1 K232A		MFA	Modicana cows	Italy	[119]
PRLR (BTA14)	g.38948871C > T (5′ flanking region) g.38949011G > A (5′ flanking region) g.39115345 T > C(Exon4)		MFA			[120]
PRLR	g.39115344G > A (Exon4)	Serine- asparagine	MFA			[120]
CHUK (BTA26)	g.21008688G > T (5′ flanking region) g.20966385C > G (3′ UTR) g.20966354C > T(3′ UTR)		MFA	Chinese Holstein	China	[120]
MOGAT1 (BTA2)	g.111599360A > G T (5′ flanking region) g.111601747 T > A T (5′ flanking region)		MFA	Chinese Holstein	China	[120]
MINPP1 (BTA26)	g.9206582C > T (3′ UTR) g.9207070A > G (intron 5)		MFA	Chinese Holstein	China	[120]
CPM (BTA5)	g.45079507A > G-5′ flanking region rs208252716 g.45080228C > A-5′ flanking region rs109638242 g.45080335C > G-5′ flanking region rs136799678 g.45162113G > A 3-UTR rs134841257 g.45163633G > T 3- flanking region rs110822514 g.45164215A > G-3- flanking region rs462818932 g.45164996A > G-3- flanking region rs382501675		MFA	Chinese Holstein	China	[121]
CPM	apmap49848-BTA-106779 (Intron 2)		MFA	Chinese Holstein	China	[30]
LIPK (BTA26)	g.10428101G > A rs110322221 (5-UTR) g.10449831C > A rs42774527 (Exon 11) g.10214117A > C rs41606812 (5′ flanking region) g.10217380C > A rs211373799 (5-UTR) g.10247997T > C rs42107056 (3′ UTR)		MFAs	Chinese Holstein	China	[122]
LIPJ (BTA26)	g.10250098C > T (3- flanking region) rs42107122 g.10250120A > G ss158213049726 (3- flanking region) g.10251075G > T rs209219656 (3- flanking region) g.10251111T > C rs42107114 (3- flanking region)		MFAs	Chinese Holstein	China	[122]
DGAT1 (BTA14)	DGAT1 (K232A)		MFY	Dutch Holstein	Israel	[123]

Table 3. *Cont.*

Gene (Location)	Polymorphism (Location)	Change in Amino Acid Sequence	Production Trait	Breed	Country	Author
DGAT1	DGAT1 (K232A)		MPTs	Holstein	USA	[124]
DGAT1	DGAT1 (K232A)		MPTs	Irish Holstein	Ireland	[125]
DGAT1	rs109663724		PY, FY, MY		USA	[126]
DGAT1	rs132699547 rs135423283 rs135576599 rs13675432		PY, FY	Holstein	USA	[126]
DGAT1	DGAT1 (K232A)		MPTs + milk coagulation properties	Italian Holstein	Italy	[127]
DGAT1	DGAT1 (K232A)		MFY, MPY, MFAs	Holstein	Netherlands	[128]
DGAT1	DGAT1 (K232A)		MPTs, LC	Holstein	Netherlands	[68]
DGAT1	DGAT1 (K232A)		MFAs	Holstein–Friesian, Jersey, Frisón Negro, Montbeliarde, and Overo Colorado	Chile	[67]
DGAT1	DGAT1 (K232A)		MPTs	Holstein	Netherlands	[65]
DGAT1	DGAT1 (K232A)		MPTs	Borgou and White Fulani cattle	Benin	[66]
DGAT1	DGAT1 (K232A)		MPTs	Holstein	Czech Republic	[129]
DGAT1	DGAT1 (K232A)		MFAs	Polish Holstein	Poland	[64]
DGAT1	DGAT1 (K232A)		MPTs	Polish Holstein	Poland	[130]
DGAT1	DGAT1 (K232A)		Milk metabolome and proteome	Holstein	Netherlands	[131]
DGAT1	DGAT1 (K232A)		MFAs	Holstein	Netherlands	[132]
DGAT1	DGAT1 (K232A)		FY, PY	Holstein	Germany	[133]
DGAT1	DGAT1 (K232A)		MPTs	Polish Holstein	Poland	[134]
DGAT1	DGAT1 (K232A)		FP, MFAs	Romanian Holstein	Romania	[135]
DGAT1	DGAT1 (K232A)		MFAs	Holstein	Netherlands	[69]
DGAT1	DGAT1 (K232A)		MFAs	Holstein	Netherlands	[136]
DGAT1	DGAT1 (K232A)		FY, PY, MY	Holstein	Netherlands	[71]
DGAT1	DGAT1 (K232A)		MFAs	Holstein	Netherlands	[137]
DGAT1	DGAT1 (K232A)		MPTs	Holstein cross Normande	France	[70]
DGAT1	DGAT1 K232A		FC, PC	indigenous Ongole cattle, Indian Jersey, Holstein	India	[138]
DGAT1	rs109421300 G > A (5′flanking region)		FP	Holstein	China	[1]
JAK2 (BTA8)	rs210148032 C > T(exon 16)		PP	Holstein	China	[1]
JAK2	JAK2/RsaI (rs110298451)		PY	Polish Holstein, Montbeliarde, Simmental, Jersey	Poland	[139]
ELOVL6 (BTA6)	g16379651A > G *ELOVL6*-Intron 3 g16458976A > G *ELOVL6*-Intron 3		MY	Holstein	China	[3]
	g16511290A > G *ELOVL6*-3′ UTR		MY, MFC (%)	Holstein	China	[3]
ACSL1 (BTA27)	5′UTR-ACSL1-g.20523C > G ACSL1-g.35651G > A- Intron 2		PC (%)	Holstein	China	[140]
ACSL1	ACSL1-g.35446C > T- Intron 2 ACSL1-g.35651G > A- Intron 2 g.51472C > T- ACSL1-Intron 11		TDMY (kg), FC (%), PC (%)	Holstein	China	[140]
AGPAT6 (BTA27)	BovineHD2700010331 g.36175805C.T (Intron 1) ARS-BFGL-NGS-57448 g.36155097C.T (5-UTR exons)		MFY	New Zealand Holstein-Friesian cross Jersey	Newzealand	[95]

Table 3. *Cont.*

Gene (Location)	Polymorphism (Location)	Change in Amino Acid Sequence	Production Trait	Breed	Country	Author
AGPAT3 (BTA1)	g. 146702957G > A rs210638665 (5′ flanking region) g. 146704373A > G rs209442459 (5′ flanking region) g. 146704618A > G rs110551271 (5′ flanking region) g. 146704699G > A rs110278717 (5′ flanking region)		MFAs	Holstein	China	[94]
AGPAT3	g.28731 A > G g.12264 C > T		PP (%), FP (%), MY	Holstein	China	[93]
ATPase 6 (BTA20)	m.8308A > G (Exon 2)		MFY	Holstein	China	[141]
BoLA (BTA23)	BoLA-DRB3.2 (exon 2)		Milk microbiota	Holstein	Canada	[142]
CSN3 (BTA6)	g.10993T > A (exon 4) g.10888T > C (exon 4) g.10924C > A (exon 4) g.10985G > A (exon 4)	Iso-Thr Ala-Asp Ala-Ala	PP (%), FP (%)	Holstein	China	[63]
CSN3	g.10944A > G(exon 4)	Serine > Glycine	MY, FY, FP (%), PY	Holstein	China	[63]
CSN3	g.12703T > G		MY, FY, PY, PP(%)	Holstein	China	[63]
GHR (BBTA20)	GHR-F279Y polymorphism	phenylalanine to tyrosine	MY, PC (%), FC (%), LC (%)	Holstein	Germany	[143]
HSP90AB1 (BBTA23)	SNP g.4338T > C		MY	Frieswal, Sahiwal	India	[144]
HTR1B (BTA9)	rs207969357 g.17303383G > T (Exon 1)	Alanine to Serine	MFAs	Holstein	China	[145]
HTR1B	rs207969357 g.17307103A > T (Promoter) rs476055046 g.17305206 T > G (Promoter) rs476055046 g.17303761C > T (Promoter) rs208945882 g.17303042C > G (Exon-1)		MFAs	Holstein	China	[145]
IGF2 (BTA29)	g.8656C > T-Exon 2 g.24507G > T-Exon 10		FY, PY, PC	Polish Holstein	Poland	[146]
IGF2	rs42196909 IGF2.g-3815A > G rs42196901		MY, PY	Irish Holstein	Ireland	[147]
IGFBP2 (BTA9)	rs133488718-Intron 3 rs133235938- Intron 5		MY	Holstein	UK	[148]
PDE9A (BTA2)	c.-2012 T > C (rs42140305) c.-2005 A > G (rs381951806)		MY, PY	Holstein	China	[149]
LAP3 (BTA6)	g.24564G > A (ss196003366) g.24794T > G g.24803T > C g.24846T > C g.25415T > C		MFP (%), PP (%)	Holstein	China	[150]
Lipin 1 (BTA11)	g.86129263C > G rs211527179-5-flanking region		FY, FP (%), PY	Holstein	China	[151]
Lipin 1	c.637T > C rs110871255-exon 5	Methionine-thr	MY, FP (%),PY	Holstein	China	[151]
Lipin 1	c.708A > G rs110161110-exon 5	Thr-Ala	MY, PY	Holstein	China	[151]
Lipin 1	c.1521C > T rs207681322-exon 8	Proline-Serine	MY, FY, FP (%), PY	Holstein	China	[151]
Lipin 1	c.1555A > C rs137642654-exon 8	Histidine-Proline	MY, FP (%),PY	Holstein	China	[151]
Lipin 1	g.86049523C > T rs135886289-3-flanking region g.86049389C > T rs109039955-3-flanking region		MY, FY, PY, PP (%)	Holstein	China	[151]
Leptin (BTA4)	accession number MN119554 SNP	p.Ala80Val	MFAs	Holstein Friesian × Jersey dairy cows	Newzealand	[152]

Table 3. *Cont.*

Gene (Location)	Polymorphism (Location)	Change in Amino Acid Sequence	Production Trait	Breed	Country	Author
MBL (BTA26)	g. 2686T > C-Exon 2 g.2651G > A-Exon 2		FC (%), PC (%)	Bohai Black Chinese Holstein Luxi Yellow	China	[153]
MBL	g.1164 G > A (Exon 3)	Proline-Glutamine	FC (%), PC (%)	Chinese Holstein	China	[154]
OLR 1 (BTA5)	SNP10497 A > C (3′ UTR)		PC (%)	Israeli-Holstein	Israel	[155]
PRKG1 (BTA26)	g.8344262A > T rs109571301-5′ flanking region g.6904047G > T rs478962267-3′ UTR g.6903810G > A rs444193880-3′ UTR g.6903365C > A rs42630538-3′ UTR g.6902878 T > G rs136888798-3′ UTR g.6901713 T > G rs381717383-3′ flanking region		MFAs	Chinese Holstein	China	[156]
Prolactin (BTA23)	-1043A > G (Promoter) -402A > G (Promoter) + 8398G > A (Exon 4)		MY, MFC (%)	Chinese Holstein	China	[96]
Prolactin	g.7545G > A(Intron 4)		MY	Chinese Holstein	China	[97]
SCAP (BTA23)	ss526061914 (5-UTR/Exon 1)		MY, MFAs	Holstein	US	[157]
INSIG1 (BTA4)	ss526061846 (Exon 4)	L852P	MY, MFAs	Holstein	US	[157]
SREBF1 (BTA19)	ss526061830 (Exon 14)		MFAs	Holstein	US	[157]
SLC27A1(BTA1)	SNP-112T > C		MY	Chinese Holstein	China	[158]
SLC27A6 (BTA1)	g.390C > T ss672469900-Exon1 g.15975T > C ss672469898-Exon2		MFAs	Holstein	US	[159]
SLC27A6	g.242A > T ss672469901-Exon1	Lysine81methionine	MFAs	Holstein	US	[159]
FABP4 (BTA14)	g.3711G > C ss672469893-Exon3 g.3691G > A ss672469894-Exon3	Valine110Methionine	MFAs	Holstein	US	[159]
TLR4 (BTA8)	c.-226 G > C rs 29017188 c.2021 C > T rs 8193069		MY, FC (%), PC (%), LCA (%)	Chinese Holstein	China	[160]
TLR4	c.2021 C > T	Threonine-isoleucine	MY, FC	Chinese Holstein	China	[161]
Lactoferrin (BTA22)	SNPs -270 T > C SNP-156 A > G		FC (%), PC (%), LCA (%)	Chinese Holstein	China	[162]
Transferrin (BTA1)	g.-1748 G > A ss250608649-5-Flanking region g.14037A > G ss250608651-Exon 8		MY, PC (%)	China Holstein Luxi Yellow Bohai Black	China	[163]
SCL2A12 (BTA1)	g.72224078C > G–5-Flanking region		MY, FC (%), PY, LY, LC (%)	Polish Holstein	Poland	[164]
SCL5A1 (BTA1)	g.70571253A > G (Promoter)		MY, FC (%), PY, LY, LC (%)	Polish Holstein	Poland	[164]
Leptin (BTA4)	rs29004509-exon 3		MY	indicine and taurine crossbred (Karan Fries)		[165]
LALBA (BTA5)	g.31183170T > C-promoter region		LY, MY	Polish Holstein	Poland	[166]
PIK3R1 (BTA20)	g.4453141 T > G-5′flanking region rs207593520 c.1505G > A-3′UTR rs208460068 g.4448024C > T-3′flanking region rs209154772 g.4447105C > G-3′flanking region rs210000760		MY, FC (%), PY, FY, PC (%)	Chinese Holstein	China	[6]

Table 3. *Cont.*

Gene (Location)	Polymorphism (Location)	Change in Amino Acid Sequence	Production Trait	Breed	Country	Author
PIK3R1 (BTA20)	c.208G > A-5′UTR rs42590258 GG 0.41 c.2776 T > C-3′UTR rs210389799 c.2962 T > C-3′UTR rs208819656 c.6275 T > A-3′UTR rs41255622 g.11323546C > T-3′flanking region rs133655926 g.11323118G > A rs211408208-3′flanking region		MY, FC (%), PY, FY, PC (%)			[6]
GH (BTA19)	GHp.L127V (Exon 5)		MFAs, MY	Modicana cows	Italy	[167]
TMEM232 (BTA7) *HCN4 (BTA9)* *ATP8A2 (BTA12)* *LOC524642 (BTA29)* *LOC524642*	rs43708473 rs110025880 rs109784719 rs42169108 rs43099931		MY	Holstein	Germany	[168]
HAL (BTA5)	ss974768522 (Promoter) ss974768523 (Exon 1) ss974768527 (Exon8) ss974768525 (Exon5)	N42N I156I Gly228Glu	Milk production traits	Chinese Holstein	China	[169]
GALE (BTA2)	g.2114A > G-5′-UTR ss1996900612 g.2037G > A-5′-UTR ss1996900613 g.3836 G > C-Introm 9 rs211659075		MY, FY, PY, PP	Chinese Holstein	China	[170]

MY: milk yield; TDMY: Test-day milk yield; PC: Protein content; MFY: Milk fat yield; MFC (%): Milk fat content (%); MPTs: Milk protein traits; LY:Lactose Yield; LC: Lactose contents; FP: fat percentage, PY: protein yield, PP: protein percentage, MFA: Milk fatty acids; LC: lactose content; LL: Lactation length; milk medium-chain fatty acids (MCFAs); 3′ untranslated region (UTR); BTA21: Bos Taurus autosomal chromosome 21; *Serpin peptidase inhibitor, clade A (SERPINA1); histidine ammonia-lyse gene (HAL); (Sterol regulatory element-binding protein-1 (SREBP1); UDP-galactose-4-epimerase (GALE); acetyl-CoA carboxylase beta (ACACB); SREBP cleavage-activating protein (SCAP); insulin-induced protein 1 (INSIG1);insulin-induced protein 2 (INSIG2); membrane-bound transcription factor protease, site 1 (MBTPS1); membrane-bound transcription factor protease, site 2 (MBTPS2); stearoyl coenzyme-A desaturases (SCD1 and SCD5); thyroid hormoneinducible hepatic protein gene (THRSP); UDP-glucose dehydrogenase (UDPH); Mitogen activated protein kinase kinase kinase kinase (MAP4K4); insulin-like growth factor receptor 2 (IGF2R); fatty acid synthase (FASN); peroxisome proliferator-activated receptor gamma, coactivator 1 alpha (PPARGC1A); ATP-binding cassette, sub-family G, member 2 (ABCG2); insulin-like growth factor 1 (IGF1); leptin receptor (LEPR); 1-acylglycerol-3-phosphate Oacyltransferas 3 (AGPAT3); Conserved helix-loop-helix ubiquitous kinase (CHUK); Multiple inositol-polyphosphate phosphatase 1 (MOGAT1); Multiple inositol-polyphosphate phosphatase 1 (MINPP1); carboxypeptidase M (CPM); enoyl-CoA hydratase, short chain 1 (ECHS1); Fatty acid desaturase 1 (FADS1) and 2 (FADS2); lipase family member K (LIPK); lipase family member J (LIPJ); Janus kinase 2 (JAK2); ELOVL6:Fatty Acid Elongase 6; ACSL1:acyl-CoAsynthetase 1; bovine major histocompatibility complex (BoLA); Iso:Isoleucine; Thr: Threonine; Ala: Alanine; Asp: Aspartic acid; CSN3:kappa casein; GHR: growth hormone receptor; HTR1B:hydroxytryptamine receptor 1B; IGF2: Insulin-like growth factor 2; IGFBP2:Insulin-like growth factor binding protein-2; PDE9A:Phosphodiesterase9A; MBL: Mannan-binding lectin; OLR 1: oxidized low-density lipoprotein (lectin-like) receptor 1; PRKG1: protein kinase, cGMP-dependent, type I; SREBF1: sterol regulatory element binding transcription factor 1; SLC27A1: solute carrier family 27 member 1″ protein;TLR4: Toll-like receptor 4; LALBA: Alpha-lactalbumin; phosphoinositide-3-kinase regulatory subunit 1 (PIK3R1); dual specificity phosphatase 1 (DUSP1); Growth hormone (GH);Long-chain acyl-CoA synthetase 1 (ACSL1); protein tyrosine kinase 2 (PTK2).*

7. Conclusions

In the current review, we documented several genes associated with milk production traits in dairy cattle. Moreover, many SNPs within candidate genes were highlighted in the current review, which could be a useful addition to the genetic markers linked to the improvement of milk production traits in dairy cattle. There are still many candidate genes reported through GWAS studies, RNA-seq and DNA-seq need further validation in dairy cattle before selecting them as genetic markers in cattle breeding.

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