

Systematic Review of Single Nucleotide Polymorphisms of Cattle Beta-Lactoglobulin Gene and their Association with Milk Production Traits

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Abstract: The application of molecular genetics technology to pinpoint certain DNA markers associated with commercially significant features is highly anticipated since it has the potential to enhance the effectiveness of breeding programs by selecting young animals early for use as future breeding stock. One of the main genes expressed in bovine milk is the Beta-Lactoglobulin Gene (β LG), and its polymorphism can be used as a useful molecular marker for characteristics related to milk production. However, there is no systematic review providing information on the β LG variations in form and their relationship with characteristics of milk production in cattle. Hence, this study's objective was to review the Single Nucleotide Polymorphisms (SNPs) of β LG and their relationship with milk production traits in cattle systematically. As stated by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, this systematic review was carried out. Databases including Science Direct, Google Scholar, PubMed, and Web of Science were evaluated systematically using 'polymorphisms/single nucleotide polymorphisms/genetic polymorphisms/ genetic effect/genetic variants', 'beta-lactoglobulin gene', 'Milk production traits/milk components' and 'cattle' as keywords. Articles that were identified in the electronic databases were one hundred and thirty-two ($n = 132$). A total of thirty-three ($n = 33$) studies were included in this study after screening. The findings of this systematic review indicated 11 SNPs (1810C>T, 3984A>G, 968C>A, 5239C>A, 5240A>C, 5305C>T, 301T>C, 390C>T, 435C>G, 424T>G and 422G>A) were identified with no similar SNPs identified by the reviewed articles. These findings suggest that SNPs 1810C>T, 968C>A, 5239C>A, 5240A>C, 5305C>T, 301T>C, and 390C>T are associated with some of the characteristics of milk production in cattle. This study concludes that the beta-lactoglobulin gene influences fat percentage, milk, lactose, fat, and protein yield in cattle. However, more studies need to be conducted for further validation of the identified SNPs since no articles identified the same SNPs. Furthermore, identified SNPs might be used as a potential molecular marker for the genetic enhancement of features related to milk output in cattle breeding.

Keywords: Dairy Cattle, Milk Production Traits, Beta-Lactoglobulin Gene, Single Nucleotide Polymorphisms

Introduction

Milk is a vital component of food preparations for humans and a vital supply of nutrients for lactating calves (Zaglool *et al.*, 2016). However, milk production characteristics (lactose, protein, fat, and milk yield) of cattle such as Holstein Friesian, Jersey, Sahiwal cattle

breeds and Girolando cows require genetic improvement (Zaglool *et al.*, 2016; Badola *et al.*, 2019; Barbosa *et al.*, 2019). Each of the included articles offers a distinct conclusion regarding how β LG affects the milk production traits of cattle. Hence, the current systematic review is needed to combine their results to give a summarized conclusion regarding the possibility of this

gene being used as a genetic marker. Single Nucleotide Polymorphisms (SNPs) in milk-related genes have sparked a lot of attention in the dairy business and breeding of animals because of the connection between genes associated with milk and characteristics that affect milk output, one of the milk-related genes is Beta-Lactoglobulin (β LG) gene (Dogru, 2015). The primary whey protein gene, β LG, is linked to varying levels of beta-lactoglobulin protein in the milk of cattle and it enables identical protein, long-chain fatty acid, and protein binding (Dogru, 2015). This gene has a high influence on the amount of whey protein content, milk, and fat content produced in milk (Jawasreh *et al.*, 2019). It was proposed that β LG variations could be helpful in programs of indirect selection to enhance the qualities of milk production, such as the yields of milk and fat, the ratio of fat to protein, and so on Ozdemir and Doğru (2007). This review summarizes the regions of the SNPs of β LG, allelic and genotypic frequencies, and the SNP's connection with milk production characteristics of cattle since there is no systematic review providing the above-mentioned information. This systematic study was done to shed light on the linkage between the beta-lactoglobulin gene with the characteristics of dairy cattle's milk production. This systematic review will help researchers and dairy cattle farmers to know the association that single nucleotide polymorphism of β LG has on milk production characteristics of dairy cattle. This systematic review will also aid in highlighting and detailing the recent developments and discoveries about the SNPs of β LG and their potential use as genetic markers during the breeding of dairy cattle for marker-assisted selection.

Methods

Eligibility Criteria

Finding the Population, Exposure and Outcomes (PEO) components of the research question is essential to doing a systematic review, as stated by Bettany-Saltikov (2010). The population was classified as "cattle," with "Polymorphisms" and "milk production traits" as their exposure and results. A preliminary search of the PEO components on Google Scholar, PubMed, Web of Science, and Science Direct databases was done before deciding to carry out the study.

Search Strategy for Identification of Relevant Studies

Both authors independently conducted a publication search in search engines such as PubMed, Science Direct, Google Scholar, and Web of Science up to 20th February 2023. 'polymorphisms/single nucleotide polymorphisms/genetic polymorphisms/genetic effect/Genetic variants', 'beta-lactoglobulin gene', 'milk production traits/milk components' and 'cattle' were used as key terms when performing publication search.

Inclusion Criteria

The search approach was used to find titles and abstracts, which were then manually screened to find studies that might be relevant. Articles were included in this systematic review provided: They included associations between milk production traits and the beta-lactoglobulin gene in cattle.

Exclusion Criteria

Studies that were not published in English, the ones using a different species other than cattle, missing one of the keywords, not assessed association to milk production traits, full-text not accessible, no data on the relationship between milk production traits and recognized genotypes and review papers were excluded. Duplicate studies were also excluded.

Data Extraction

The investigators (Makamu, TC, and Tyasi, TL) collected data and studied content on their own and an agreement was reached concerning all key items.

Results

Searched Results

Articles that were identified in the electronic databases were one hundred and thirty-two ($n = 132$). Studies that remained after the exclusion of duplicates were sixty-five ($n = 65$). Through screening of the titles and abstracts in the paired selection, about forty-two ($n = 42$) articles that weren't relevant to our focus were removed. Among the fifty-three ($n = 53$) studies that were selected for full reading nineteen ($n = 19$) studies that did not fulfill the requirements for eligibility were excluded. Finally, a total of thirty-three ($n = 33$) studies were included in our systematic review (Fig. 1).

Characteristics of Articles Included

The characteristics of the thirty-three ($n = 33$) selected studies are summarized in Table 1. The studies included ranged from 1984-2022, with about three ($n = 3$) studies from 1984-1990, five ($n = 5$) studies from 1991-2000, seven ($n = 7$) studies from 2001-2019, and eighteen ($n = 18$) studies ranging from 2011-2022. These studies were from twenty ($n = 20$) different countries, Turkey ranking first with five ($n = 5$) studies, followed by Canada with four ($n = 4$) studies, Then Italy and China with three ($n = 3$) studies each, Germany and India had two ($n = 2$) studies each, the other countries only had one study each as shown in Table 1. A total of 15 different breeds including Holstein, Simmental, Bulgarian black pied, Girolando, red and white, brown Swiss, black and white, Finnish

Arshire, Italian Brown, Sahiwal, East Anatolian Red, Frieswal, Mazandarani, Sarabi, and Golpaygani were used within the reviewed articles. Out of 33 included articles, 21 of them used the Holstein cattle breed followed by 3 of the Simmental cattle breed. The number of animals used ranged from 21-20928, with thirteen (n = 13) studies ranging from 100-200. About 58% of studies used the Holstein cattle breed. About three studies (n = 3) were published by the same author, whereas all the other authors wrote only one article each. PCR-RFLP was the most often utilized genotyping technique, being employed in sixteen (n = 16) research papers.

Publication by Country

Figure 2 displays the publication by country of included studies in the current systematic review. The results indicated that thirty-three (n = 33) studies were published in different countries worldwide. These studies were from twenty (n = 20) different countries, Turkey ranking first with 5 out of 33 studies, followed by Canada with 4 out of 33 studies, Italy and China with 3 studies each out of 33, Germany and India with 2 studies each out of 33, 14 countries {Brazil; Netherlands; New Zealand; Bulgaria; Eastern Finland; Sweden; Pakistan; Thailand; Lithuania; Romania; Israel; North Kazakhstan; Northern Greece; Egypt} had 1 study each out of 33 studies.

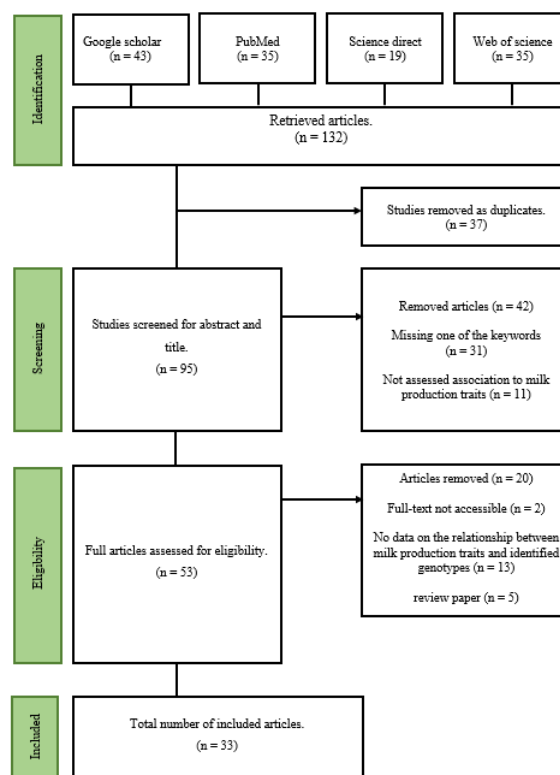


Fig. 1: A flow chart that illustrates the procedure for choosing studies

Table 1: Characterization of included studies

Author	Year	Country	Breed	Sample size	Milk production traits	Genotyping method
Ng-Kwai-Hang <i>et al.</i> (1984)	1984	Canada	Holstein	3870	FY, PP, FP, MY and PY	PGE
Ng-Kwai-Hang <i>et al.</i> (1986)	1986	Canada	Holstein Friesian	1908	MY, PP and FP	VPGE
Ng-Kwai-Hang <i>et al.</i> (1990)	1990	Canada	Holstein	8000	FY, PP, FP, MY and PY	ETO
Hill (1993)	1993	New Zealand	Holstein Friesian	349	TP, fat and TS	PGE
Ron <i>et al.</i> (1994)	1994	Israel	Holstein	113	FY, PP, FP, MY and PY	PCR-RFLP
Falaki <i>et al.</i> (1997)	1997	Italy	Simmental	427	FY, PP, FP, MY and PY	PCR-RFLP
Lundén <i>et al.</i> (1997)	1997	Sweden	Red and white, Holstein	645	MY, PY, FY, LY, PP, FP and LP	AAPAGE
Ikonen <i>et al.</i> (1999)	1999	Eastern Finland	Finnish Ayrshire	20928	FY, PP, FP, MY and PY	IFPG
Robitaille <i>et al.</i> (2002)	2002	Canada	Holstein	40	MY, CP, FY and LY	GEUA
Tsiaras <i>et al.</i> (2005)	2005	Northern Greece	Holstein	350	MY, PY, FY, FP and PP, LY and LP	AAPGE
Zhang <i>et al.</i> (2006)	2006	China	Holstein	161	MY, PP, FP, SCS and SCC	PCR-RFLP
Ozdemir and Doğru (2007)	2007	Turkey	Brown Swiss, Holstein, East Anatolian red	169	MY, FP and FY	HSGE
Botaro <i>et al.</i> (2008)	2008	Brazil	Girolando, Holstein	434	Fat, lactose and total solids	PCR-RFLP
Heck <i>et al.</i> (2009)	2009	Netherlands	Holstein-Friesian	1912	FY, PP, FP, MY and PY	CZE
Bonfatti <i>et al.</i> (2010)	2010	Italy	Simmental	2167	FY, PP, FP, MY and PY	RP-HPLC
Czerniawska-Piatkowska <i>et al.</i> (2011)	2011	Germany	Holstein Friesian	102	FY, PP, FP, MY and PY	PCR-RFLP
Gurcan (2011)	2011	Turkey	Black and White	90	MY	SEMUR
Hristov <i>et al.</i> (2011)	2011	Bulgaria	Bulgarian black pied	21	MY, FP and PP	PCR-RFLP
Yang <i>et al.</i> (2012)	2012	China	Holstein	82	MY, PP and FP	PCR-SSCP
Zakizadeh <i>et al.</i> (2012)	2012	Germany	Mazandarani, Sarabi, Golpaygani, Holstein	406	MY, FY and FP	PCR-RFLP
Mancini <i>et al.</i> (2013)	2013	Italy	Italian brown	561	MY, PY and FY	SNaPshot
Mir <i>et al.</i> (2014)	2014	Pakistan	Sahiwal	120	MY	PCR-RFLP
Tolenkhomba <i>et al.</i> (2014)	2014	India	Sahiwal	157	MY, FY, FP, SNFY and SNFP	PCR-RFLP
Alim <i>et al.</i> (2015)	2015	China	Holstein	766	FY, PP, FP, MY and PY	MALDI-TOF
Dogru (2015)	2015	Turkiye	Brown Swiss	129	MY, FP and FY	HSGE
Molee <i>et al.</i> (2015)	2015	Thailand	Crossbred Holstein	231	MY, FP, PP, SNF and TS	PCR-RFLP
Singh <i>et al.</i> (2015)	2015	India	Friesian	126	MY and SCC	PCR-RFLP
Zaglool <i>et al.</i> (2016)	2016	Egypt	Holstein Friesian	200	MY, FP, PP, LP, and SNFP	PCR-RFLP
Neamt <i>et al.</i> (2017)	2017	Romania	Simmental	114	FY, PP, FP, MY and PY	PCR-RFLP
Safronova <i>et al.</i> (2017)	2017	North Kazakhstan	Black and white	100	MY, PP and FP	PCR-RFLP
Morkūniene <i>et al.</i> (2018)	2018	Lithuania	Holstein	147	MY, PY and PP	PCR-RFLP
Soyudal <i>et al.</i> (2019)	2019	Turkey	Holstein Friesian	189	MY, PY, FY, FP, PP, LP, LY, TS and SP	PCR-RFLP
Semerici and Balcioglu (2002)	2022	Turkey	Holstein	517	MY	PCR-RFLP

Lactose yield, MY (MY-LY) Yield of milk, (PY) Yield of Protein, (FY) Yield of Fat, (PP) Percentage of Protein, (FP) Percentage of Fat, (SNF) Solids Not Fat, (TS) Total Solids, (CP) Crude Protein, (SCS) Somatic Cell Score, (SP) Solid Percentage, (SCC) Somatic Cell Count, (SNFY) Solid Not Fat Yield, (SNFP) Solids Not Fat Percentage, (LP) Lactose Percentage, (TP) Total Protein, (PCR-RFLP) Restricted Fragment Length Polymorphism using Polymerase Chain Reaction (HSGE) Horizontal Starch-urea Gel Electrophoresis, (SEMUR) Starch Gel Electrophoresis containing urea and mercaptoethanol, (CZE) Capillary Zone Electrophoresis, (PGE) Polyacrylamide Gel Electrophoresis, (IFPG) Isoelectric Focusing in Polyacrylamide Gels, (VPGE) Vertical Polyacrylamide Gel Electrophoresis, (AAPAGE) Alkaline and Acidic PAGE, (PCR-SSCP) Single Strand Conformation Polymorphism using Polymerase Chain Reaction, (RP-HPLC) High Performance Liquid Chromatography using Reversed Phase, (GEUA) Gel Electrophoresis Under Alkaline Ph, (ET) Electrophoretic Technique, (AAPGE) Alkaline and Acidic Polyacrylamide Gel Electrophoresis

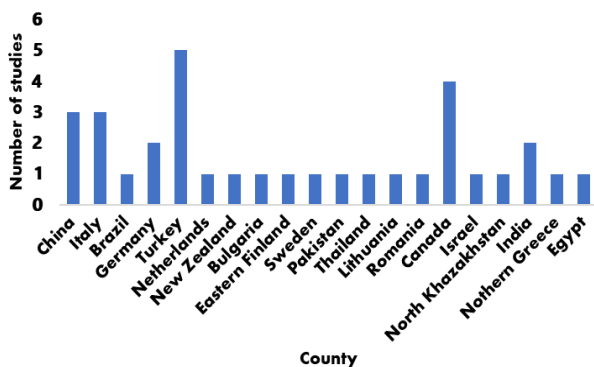


Fig. 2: Publication by country

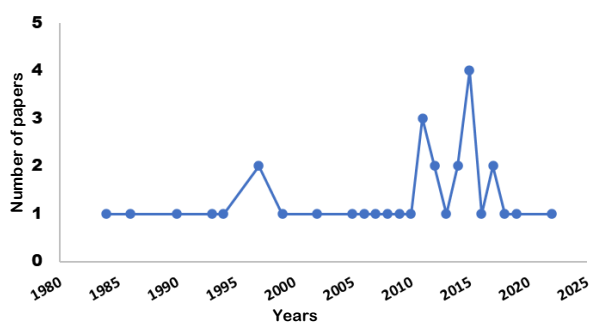


Fig. 3: Publication by year

Publication by Year

Figure 3 indicates the publication by year of included studies (n = 33) in the current systematic review. The findings showed that included studies were published from the year 1984-2022. Majority of the studies were published in 2015 with 4 out of 33 followed by 2011 with 3 out of 33 (Czerniawska-Piatkowska *et al.*, 2011; Gurcan, 2011; Hristov *et al.*, 2011), 4 years (1997; 2012; 2014; 2017) included 2 studies each out of 33, 18 years (1984; 1986; 1990; 1993; 1994; 1999; 2002; 2005; 2006; 2007; 2008; 2009; 2010; 2013; 2016; 2018; 2019; 2022) included 1 study each out of 33.

Single Nucleotide Polymorphisms (SNPs) Found and Regions

Table 2 lists the regions that include the single nucleotide polymorphisms (SNPs) that were identified. Six articles identified SNPs and their regions out of 33 reviewed articles. Three articles (50%) out of six articles found SNPs in exon 4. Two articles (33%) out of six articles did not identify the DNA region studied for the SNPs. The findings showed no similar SNPs identified in the reviewed articles.

Table 2: Single Nucleotide Polymorphisms (SNPs) and regions

Author	Breed	N	Region	Identified SNPs
Alim <i>et al.</i> (2015)	Holstein	766	Exon 3	1810C>T
Heck <i>et al.</i> (2009)	Holstein-Friesian	1912	-	3984A>G
Mancini <i>et al.</i> (2013)	Italian Brown	561	-	968C>A
Yang <i>et al.</i> (2012)	Holstein	82	Exon 4	5239C>A, 5240A>C, 5305C>T
Zaglool <i>et al.</i> (2016)	Holstein Friesian	200	Exon 4	301T>C, 390C>T
Zakizadeh <i>et al.</i> (2012)	Mazandarani, Sarabi, Golpaygani, Holstein	406	Exon 4	435C>G, 424T>G, 422G>A

Genotypic Frequencies

Table 3 indicates the genotypic frequencies from different reviewed articles. Out of 30 articles, 27 (90%) of them showed 3 genotypes per SNP, whereas 3 (10%) articles showed 2 genotypes per SNP. The discovered genotypic frequencies from the reviewed articles ranged from 0.017-0.89.

Gene Frequencies

Identified allelic frequencies from different reviewed articles are presented in Table 4. Out of 33 collected reviewed articles, 30 of them were clear about allelic frequencies, whereas 3 were not. The discovered allelic frequencies from the reviewed articles ranged from 0.09-0.91.

Association Between Genotypes and Milk Production Characteristics

Table 5 displays the results of the genetic association study for milk production traits. Each reviewed article examined the relationship between variables related to milk production and genotypes. The reviewed articles examined 16 different aspects of milk production, such as Total Protein (TP), Milk Yield (MY), Solids Not Fat (SNF), Solid Not Fat Yield (SNFY), Crude Protein (CP), Somatic Cell Score (SCS), Solid Not Fat Percentage (SNFP), Somatic Cell Count (SCC), Solid Percentage (SP), Protein Yield (PY), Fat Yield (FY), Lactose Yield (LY), Protein Percentage (PP), Lactose Percentage (LP), Fat Percentage (FP) and Total Solids (TS). Out of 33 reviewed articles, 31 (93.93%) investigated MY with 19 (57.58%) non-significant whereas 12 (36.36%) were significantly associated with genotypes. About 20 articles (60.61%) investigated FY with 15 (45.45%) non-significant and 5 (15.15%) significantly associated with genotypes. LY, 6 (18.18%) investigated LY with 4 (12.12%) non-significant and 2 (6.06%) significantly associated with genotypes. PY, 15 (45.45%) investigated PY with 3 (9.09%) non-significant and 12 (36.36%) significantly related with the genotypes. FP, 24 (72.72%) investigated FP with 13 (39.39%) non-significant with genotypes and 11 (33.33%) significant.

Table 3: Genotypic frequencies

Author	Breed	N	Genotypic frequencies
Ng-Kwai-Hang <i>et al.</i> (1984)	Holstein	3870	AA (0.1344), AB (0.5054), BB (0.3602)
Ng-Kwai-Hang <i>et al.</i> (1986)	Holstein Friesian	1908	AA (0.1344), AB (0.5054), BB (0.3602)
Ng-Kwai-Hang <i>et al.</i> (1990)	Holstein	8000	AA (0.1073), AB (0.4931), BB (0.3996)
Hill (1993)	Friesian	349	AA (0.145), AB (0.48), BB (0.35)
Ron <i>et al.</i> (1994)	Holstein	112	AA (0.3036), AB (0.4375), BB (0.2590)
Falaki <i>et al.</i> (1997)	Simmental	427	AA (0.362), AB (0.394), BB (0.244)
Lundén <i>et al.</i> (1997)	Red and White	371	AA (0.121), AB (0.410), BB (0.469)
	Holstein	204	AA (0.235), AB (0.525), BB (0.240)
Ikonen <i>et al.</i> (1999)	Finnish Ayrshire	20928	AA (0.078), AB (0.413), BB (0.509)
Robitaille <i>et al.</i> (2002)	Holstein	40	AA (0.225), AB (0.500), BB (0.275)
Tsiaras <i>et al.</i> (2005)	Holstein	350	AA (0.284), AB (0.471), BB (0.245)
Zhang <i>et al.</i> (2006)	Holstein	161	AA (0.1311), AB (0.2787), BB (0.5902)
Ozdemir and Doğru (2007)	Brown Swiss	80	AA (0.2375), AB (0.5125), BB (0.2500)
	Holstein	45	AA (0.0444), AB (0.4444), BB (0.5111)
	East Anatolian Red	44	AA (0.0455), AB (0.2500), BB (0.7045)
Botaro <i>et al.</i> (2008)	Holstein	434	AA (0.3273), AB (0.2842), BB (0.3885)
	Girolando		AA (0.2115), AB (0.3397), BB (0.4487)
Heck <i>et al.</i> (2009)	Holstein-Friesian	1912	AA (0.325), AB (0.516), BB (0.159)
Bonfatti <i>et al.</i> (2010)	Simmental	2167	AA (0.306), AB (0.466), BB (0.213)
Czerniawska-Piatkowska <i>et al.</i> (2011)	Holstein-Friesian	102	AA (0.08), AB (0.40), BB (0.52)
Gurcan (2011)	Black and White	90	AA (0.37), AB (0.38), BB (0.26)
Hristov <i>et al.</i> (2011)	Bulgarian black pied	21	AB (0.57), BB (0.43)
Zakizadeh <i>et al.</i> (2012)	Mazandarani	70	AA (0.057), AB (0.40), BB (0.542)
	Sarabi	58	AA (0.017), AB (0.621), BB (0.362)
	Golpaygani	54	AA (0.056), AB (0.333), BB (0.611)
	Holstein	53	AB (0.585), BB (0.415)
Mir <i>et al.</i> (2014)	Sahiwal	120	AA (0.056), AB (0.056), BB (0.89)
Tolenkhomba <i>et al.</i> (2014)	Sahiwal	157	AB (0.32), BB (0.68)
Alim <i>et al.</i> (2015)	Holstein	766	CC (0.313), CT (0.4929), TT (0.194)
Dogru (2015)	Brown-Swiss	129	AA (0.170), AB (0.411), BB (0.419)
Molee <i>et al.</i> (2015)	Crossbred Holstein	231	AA (0.175), AB (0.535), BB (0.289)
Singh <i>et al.</i> (2015)	Frieswal	126	AA (0.238), AB (0.286), BB (0.476)
Zagloul <i>et al.</i> (2016)	Holstein Friesian	200	AA (0.22), AB (0.28), BB (0.50)
Neamt <i>et al.</i> (2017)	Simmental	114	AA (0.316), AB (0.579), BB (0.105)
Morkūniene <i>et al.</i> (2018)	Holstein	147	AA (0.183), AB (0.544), BB (0.273)
Soyudal <i>et al.</i> (2019)	Holstein Friesian	189	AA (0.1852), AB (0.5344), BB (0.2804)
Semerci and Balcioglu (2022)	Holstein	517	AA (0.23020), AB (0.4720), BB (0.2978)

Table 4: Allelic frequencies

Author	Breed	N	Allelic frequencies	
			A	B
	Holstein	204	A (0.4980)	B (0.5020)
Ng-Kwai-Hang <i>et al.</i> (1984)	Holstein	3870	A (0.3870)	B (0.6130)
Ng-Kwai-Hang <i>et al.</i> (1986)	Holstein Friesian	1908	A (0.3870)	B (0.6130)
Ng-Kwai-Hang <i>et al.</i> (1990)	Holstein	8000	A (0.3539)	B (0.6462)
Hill (1993)	Friesian	349	A (0.4000)	B (0.6000)
Ron <i>et al.</i> (1994)	Holstein	112	A (0.5224)	B (0.4778)
Falaki <i>et al.</i> (1997)	Simmental	427	A (0.5590)	B (0.4410)
Lundén <i>et al.</i> (1997)	Red and White	371	A (0.3330)	B (0.6670)
Ikonen <i>et al.</i> (1999)	Finnish Ayrshire	20928	A (0.2850)	B (0.7160)
Robitaille <i>et al.</i> (2002)	Holstein	40	A (0.4750)	B (0.5250)
Tsiaras <i>et al.</i> (2005)	Holstein	350	A (0.5200)	B (0.4800)
Zhang <i>et al.</i> (2006)	Holstein	161	A (0.2705)	B (0.7295)
Ozdemir and Doğru (2007)	Brown Swiss	80	A (0.4938)	B (0.5063)
	Holstein	45	A (0.2666)	B (0.7333)
	East Anatolian Red	44	A (0.1705)	B (0.8295)
Botaro <i>et al.</i> (2008)	Holstein	434	A (0.4694)	B (0.5305)
	Girolando		A (0.3815)	B (0.6185)

Table 4: Continue

Heck <i>et al.</i> (2009)	Holstein-Friesian	1912	A (0.5040)	B (0.4960)
Bonfatti <i>et al.</i> (2010)	Simmental	2167	A (0.5430)	B (0.4490)
Czerniawska-Piatkowska <i>et al.</i> (2011)	Holstein-Friesian	102	A (0.2800)	B (0.7200)
Gurcan (2011)	Black and White	90	A (0.5500)	B (0.4500)
Hristov <i>et al.</i> (2011)	Bulgarian Black pied	21	A (0.2900)	B (0.7100)
Zakizadeh <i>et al.</i> (2012)	Mazandarani	70	A (0.2600)	B (0.7400)
	Sarabi	58	A (0.3300)	B (0.6700)
	Golpaygani	54	A (0.2200)	B (0.7800)
	Holstein	53	A (0.2900)	B (0.7100)
Mir <i>et al.</i> (2014)	Sahiwal	120	A (0.0900)	B (0.9100)
Tolenkhomba <i>et al.</i> (2014)	Sahiwal	157	A (0.1600)	B (0.8400)
Alim <i>et al.</i> (2015)	Holstein	766	C (0.5595)	T (0.4405)
Dogru (2015)	Brown-Swiss	129	A (0.3750)	B (0.6250)
Molee <i>et al.</i> (2015)	Crossbred Holstein	231	A (0.4430)	B (0.5570)
Singh <i>et al.</i> (2015)	Frieswal	126	A (0.3810)	B (0.6190)
Zaglool <i>et al.</i> (2016)	Holstein Friesian	200	A (0.3600)	B (0.6400)
Neamt <i>et al.</i> (2017)	Simmental	114	A (0.6060)	B (0.3940)
Morkūniene <i>et al.</i> (2018)	Holstein	147	A (0.4560)	B (0.5440)
Soyudal <i>et al.</i> (2019)	Holstein Friesian	189	A (0.452)	B (0.5480)
Semerci and Balcioglu (2022)	Holstein	517	A (0.4662)	B (0.5338)

Table 5: SNPs association with milk production traits

Author	Breed	Milk production traits	Genotypes			Significant

Alim <i>et al.</i> (2015)	Holstein	MY	CT	CC	TT	*
		LY	CT	CC	TT	*
		PY	CT	CC	TT	ns
		FP	CT	CC	TT	*
		PP	CT	CC	TT	ns
Bonfatti <i>et al.</i> (2010)	Simmental	MY	AB	AA	BB	ns
		FY	AB	AA	BB	ns
		PY	AB	AA	BB	ns
		FP	AB	AA	BB	ns
		PP	AB	AA	BB	ns
Botaro <i>et al.</i> (2008)	Girolando Holstein	FY	AB	AA	BB	ns
		LY	AB	AA	BB	ns
		TS	AB	AA	BB	ns
Czerniawska-Piatkowska <i>et al.</i> (2011)	Holstein-Friesian	MY	AB	AA	BB	ns
		FY	AB	AA	BB	ns
		PY	AB	AA	BB	ns
		FP	AB	AA	BB	*
		PP	AB	AA	BB	ns
Dogru (2015)	Brown-Swiss	MY	AB	AA	BB	ns
		FY	AB	AA	BB	ns
		FP	AB	AA	BB	ns
Falaki <i>et al.</i> (1997)	Simmental	MY	AB	AA	BB	ns
		FY	AB	AA	BB	*
		PY	AB	AA	BB	ns
		FP	AB	AA	BB	ns
		PP	AB	AA	BB	ns
Heck <i>et al.</i> (2009)	Black and white Holstein-Friesian	MY	AB	AA	BB	ns
		MY	AB	AA	BB	ns
		FY	AB	AA	BB	ns
		PY	AB	AA	BB	ns
		FP	AB	AA	BB	ns
Hill (1993)	Friesian	TP	AB	AA	BB	ns
		Fat	AB	AA	BB	*
		TS	AB	AA	BB	*
Hristov <i>et al.</i> (2011)	Bulgarian black pied	MY	AB	AA	BB	*

Table 5: Continue

		FP	AB	AA	BB	*
		PP	AB	AA	BB	*
Ikonen <i>et al.</i> (1999)	Finnish Ayrshire	MY	AB	AA	BB	ns
		FY	AB	AA	BB	ns
		PY	AB	AA	BB	ns
		FP	AB	AA	BB	ns
		PP	AB	AA	BB	ns
Lundén <i>et al.</i> (1997)	Red and white Holstein	MY	AB	AA	BB	ns
		FY	AB	AA	BB	ns
		PY	AB	AA	BB	ns
		LY	AB	AA	BB	ns
		FP	AB	AA	BB	ns
		PP	AB	AA	BB	ns
		LP	AB	AA	BB	ns
Mancini <i>et al.</i> (2013)	Italian brown	MY	AB	AA	BB	*
		FY	AB	AA	BB	*
		PY	AB	AA	BB	*
Mir <i>et al.</i> (2014)	Sahiwal	MY	AB	AA	BB	ns
Molee <i>et al.</i> (2015)	Crossbred Holstein	MY	AB	AA		*
		FP	AB	AA		*
		PP	AB	AA		*
		SNF	AB	AA		ns
		TS	AB	AA		*
Morkūniene <i>et al.</i> (2018)	Holstein	MY	AB	AA	BB	*
		PY	AB	AA	BB	ns
		PP	AB	AA	BB	*
Neamt <i>et al.</i> (2017)	Simmental	MY	AB	AA	BB	*
		FY	AB	AA	BB	*
		PY	AB	AA	BB	*
		FP	AB	AA	BB	*
		PP	AB	AA	BB	*
Ng-Kwai-Hang <i>et al.</i> (1984)	Holstein	MY	AB	AA	BB	ns
		FY	AB	AA	BB	ns
		PY	AB	AA	BB	*
		FP	AB	AA	BB	*
		PP	AB	AA	BB	*
Ng-Kwai-Hang <i>et al.</i> (1986)	Holstein Friesian	MY	AB	AA	BB	*
		FP	AB	AA	BB	*
		PP	AB	AA	BB	*
Ng-Kwai-Hang <i>et al.</i> (1990)	Holstein	MY	AB	AA	BB	ns
		FY	AB	AA	BB	ns
		PY	AB	AA	BB	ns
		FP	AB	AA	BB	ns
		PP	AB	AA	BB	*
Ozdemir and Doğru (2007)	Brown Swiss Holstein East Anatolian red	MY	AB	AA	BB	ns
		FY	AB	AA	BB	ns
		FP	AB	AA	BB	ns
Robitaille <i>et al.</i> (2002)	Holstein	MY	AB	AA	BB	ns
		CP	AB	AA	BB	ns
		FY	AB	AA	BB	ns
		LY	AB	AA	BB	ns
Ron <i>et al.</i> (1994)	Holstein	MY	AB	AA	BB	ns
		FY	AB	AA	BB	ns
		PY	AB	AA	BB	ns
		FP	AB	AA	BB	*
		PP	AB	AA	BB	ns
Safronova <i>et al.</i> (2017)	Black and white	MY	AB	AA	BB	*

Table 5: Continue

		FP	AB	AA	BB	*
		PP	AB	AA	BB	*
Semerci and Balcioglu (2022)	Holstein	MY	AB	AA	BB	ns
Singh <i>et al.</i> (2015)	Frieswal	MY	AB	AA	BB	*
		SCC	AB	AA	BB	*
Soyudal <i>et al.</i> (2019)	Holstein Friesian	MY	AB	AA	BB	ns
		FY	AB	AA	BB	ns
		PY	AB	AA	BB	ns
		FP	AB	AA	BB	ns
		PP	AB	AA	BB	ns
		LY	AB	AA	BB	ns
		LP	AB	AA	BB	ns
		TS	AB	AA	BB	ns
		SP	AB	AA	BB	ns
Tolenkhomba <i>et al.</i> (2014)	Sahiwal	MY	AB	AA	BB	ns
		FY	AB	AA	BB	ns
		FP	AB	AA	BB	ns
		SNFY	AB	AA	BB	ns
		SNFP	AB	AA	BB	ns
Tsiaras <i>et al.</i> (2005)	Holstein	MY	AB	AA	BB	*
		FY	AB	AA	BB	*
		PY	AB	AA	BB	ns
		FP	AB	AA	BB	*
		PP	AB	AA	BB	ns
		LY	AB	AA	BB	*
		LP	AB	AA	BB	ns
Yang <i>et al.</i> (2012)	Holstein	MY	AB	AA	BB	*
		PP	AB	AA	BB	ns
		FP	AB	AA	BB	ns
Zagloul <i>et al.</i> (2016)	Holstein Friesian	MY	AB	AA	BB	*
		FP	AB	AA	BB	*
		PP	AB	AA	BB	*
		LP	AB	AA	BB	ns
		SNFP	AB	AA	BB	*
Zakizadeh <i>et al.</i> (2012)	Mazandarani, Sarabi, Golpaygani, Holstein	MY	AB	AA	BB	ns
		FY	AB	AA	BB	ns
		FP	AB	AA	BB	ns
Zhang <i>et al.</i> (2006)	Holstein	MY	AB	AA	BB	ns
		PP	AB	AA	BB	*
		FP	AB	AA	BB	ns
		SCS	AB	AA	BB	ns
		SCC	AB	AA	BB	ns

ns–non-significant, PY-Protein Yield, TS-Total Solids, LY-Lactose Yield, PP-Protein Percentage, MY-Milk Yield, CP- Crude Protein, SNF-Solids Not Fat, SCS-Somatic Cell Score, FP-Fat Percentage, SP-Solid Percentage, LP-Lactose Percentage, SNFY-Solid Not Fat Yield, SCC-Somatic Cell Count, SNPP-Solids Not Fat Percentage, *-Significant at $p < 0.05$, FY-Fat Yield

PP, 21 (63.63%) investigated PP with 11 (33.33%) non-significantly associated with genotypes and 10 (30.30%) significant. LP, 4 (12.12%) studied LP and all genotypes were non-significant. SNF, 1 (3.03%) investigated SNF which was non-significantly associated with genotypes. TS, 4 (12.12%) investigated TS with 2 (6.06%) non-significantly associated with genotypes and 2 (6.06%) significant. CP, 1 (3.03%) investigated CP which was non-significantly associated with genotypes. SCS, 1 (3.03%) investigated SCS which was non-significantly related to genotypes. SCC, 2 (6.06%) studied SCC with 1

(3.03%) non-significantly associated with genotypes and 1 (3.03%) significant. SP, 1 (3.03%) investigated SP which was non-significantly associated with genotypes. SNFY, 1 (3.03%) investigated SNFY which was non-significantly correlated with genotypes. SNFP, 2 (6.06%) investigated SNFP with 1 (3.03%) non-significant and 1 (3.03%) significantly associated with genotypes. TP, 1 (3.03%) investigated TP which was non-significantly associated with genotypes. Out of 33 included articles, 21 used the Holstein cattle breed, and the findings showed that 18 articles investigated MY 7 of them

showed a significant association with the identified genotypes while 11 of them showed nonsignificant association. Out of 33 included articles, 3 of them used the Simmental cattle breed and the findings showed that all the articles investigated MY, PY, FP, and PP, 2 articles showed that there was no significant association between MY, PY, FP, and PP with the identified genotypes whereas 1 showed that there was significance association. 2 articles investigated Girolando and Sahiwal which showed no significance association between MY, FY, FP and the identified genotypes. 2 articles investigated Black and White cattle breed that showed significance association between MY, FP, PP and the identified genotypes.

Discussion

The dairy sector is greatly impacted by significant quantitative traits related to milk production. Zhang *et al.* (2006). This systematic review aimed to collect information about the relationship between the Beta-Lactoglobulin Gene (β LG) Single Nucleotide Polymorphisms (SNPs) and milk production features. Polymorphism of β LG, a major gene expressed in bovine milk, can provide useful information as a milk production traits' molecular marker. Zakizadeh *et al.* (2012). After following systematic exclusion and inclusion criteria, only thirty-three articles with the sum of 45531 animals used were found in this study. The findings of this study showed that most of the studies originated from Turkey and most studies were published in 2015. The majority of included studies identified three genotypes with the gene frequency range from 0.09-0.91. The results of this systematic review showed that 6 articles out of 33 identified 11 SNPs (1810C>T, 3984A>G, 968C>A, 5239C>A, 5240A>C, 5305C>T, 301T>C, 390C>T, 435C>G, 424T>G and 422G>A) with no similar SNPs identified by reviewed articles. Alim *et al.* (2015) found that this SNP (1810C>T) had an influence on fat percentage, lactose yield, and milk yield but not on protein yield and percentage in Holstein cows. This SNP (3984A>G) was found to not be influencing fat, protein, and milk yields; percentages of protein and fat of Holstein Friesian (Heck *et al.*, 2009). Mancini *et al.* (2013) found this SNP (968C>A) to be related to the fat, protein, and milk yield of Italian Brown. These SNPs (5239C>A, 5240A>C, 5305C>T) were reported to be having an influence on milk yield, however, they had no influence on the fat and protein percentage of Holstein cows (Yang *et al.*, 2012). SNPs (301T>C, 390C>T) were related to milk yield, fat and protein percentage; and solid not fat and lactose percentage of Holstein Friesian (Zaglool *et al.*, 2016). These SNPs (435C>G, 424T>G, 422G>A) were discovered to not have any relationship with fat yield and percentage and milk yield of Sarabi, Mazandarani,

Holstein, and Golpaygani, cattle (Zakizadeh *et al.* 2012). The result of this study also shows that 21 articles that were included in this systematic review used the Holstein cattle breed. Alim *et al.* (2015), indicated that Holstein was a dairy cattle breed ranking first among the dairy cattle breeds in average milk production per cow. Somatic cell score, milk, protein and fat yields, somatic cell count, lactose yield, protein, and lactose percentage are not associated with identified genotypes whereas fat percentage and solid not fat percentage are associated with the genotypes of Holstein cattle. Based on the knowledge that we have, there are no comparisons of the other systematic review findings because this systematic review was the first one reporting on the association between SNPs of β LG with milk production characteristics of cattle. The results of this systematic review imply that the SNPs of β LG in Italian Brown, Frieswal, Bulgarian black pied, and black and white cattle breeds might be utilized as a genetic marker during breeding to enhance protein yield and proportion; fat yield and percentage; and lower somatic cell count. This systematic review adds to the body of knowledge in the way that in the case of Bulgarian Black Pied, Black and White, Italian Brown and Frieswal cattle breeds, the identified SNPs for β LG may be utilized as a genetic marker for somatic cell count, fat yield and percentage; milk yield, protein yield, and percentage; in the case of Girolando, Brown Swiss, Finnish Ayrshire, red and white, Sahiwal, total solids, protein percentage, lactose percentage, solid not a fat percentage and fat yield, the identified SNPs for β LG may not be utilized as a genetic marker for somatic cell count, protein yield, fat yield, lactose yield, and fat percentage. The limitation of this study is that out of 33 articles that investigated the relationship of β LG with milk production characteristics, only 6 of them identified the SNPs and there was no common SNP identified. Thus, not possible to conduct a meta-analysis of this data. Hence, it is highly recommended that more studies need to be conducted. The findings of this current study suggest that identified SNPs of β LG may be utilized as genetic markers to enhance characteristics of milk production for cattle.

Conclusion

This systematic review concludes that milk production characteristics of Bulgarian black pied, Black and white, Frieswal, and Italian brown cattle breeds were influenced by the beta-lactoglobulin gene and may be utilized as a molecular marker when enhancing genes responsible for milk production characteristics of these cattle breeds. For the Holstein cattle breed beta-lactoglobulin gene only influences fat percentage and solid not fat percentage, whereas for Simmental it only influences fat yield and might be utilized as a molecular marker that has the

potential to enhance genes of these milk production traits only. β LG does not influence any milk production traits on Girolando, brown Swiss, Finnish Ayrshire, red and white, Sahiwal, East Anatolian red, Mazandarani, Sarabi, and Golpaygani which showed that it cannot be utilized as a molecular marker for enhancement of genes responsible for milk production characteristics in these breeds of cattle.

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Author's Contributions

Thlarihani Cynthia Makamu: Wrote drafted manuscript, searched articles on databases, excluded and inclusion criteria of articles, data extraction, and approved the manuscript for submission.

Thobela Louis Tyasi: Revid drafted manuscript, searched articles on databases, exclusion and inclusion criteria of articles, data extraction, and approved the manuscript for submission.

Ethics

Issues around ethics, informed consent, plagiarism, and data fabrication, were considered by the authors.

Conflict of Interest

The writers claim that there isn't a conflict of interest.

Availability of Data

Upon request to the corresponding author, all data generated during this investigation are made available.

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