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Review Article

Associations Between FASN Gene Polymorphism and Milk Production Traits in the Dairy Cattle: A Systematic Review and Meta-Analysis

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Abstract

In this study, the association between FASN gene polymorphism and milk production traits in dairy cattle was examined through a systematic review and meta-analysis. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were followed for the analysis. The following databases were utilized: Google Scholar, Web of Science, PubMed, Taylor & Francis, Wiley Online Library, ResearchGate, Springer, and NCBI. The analysis was executed using the co-dominant model. Standardized mean differences (SMDs) and 95% confidence intervals were calculated using both random and fixed effect models to determine the effect size of the FASN gene polymorphism on milk production traits. All data were analysed using Stata 11.2 software. The results of the meta-analysis demonstrated statistically significant associations between FASN gene polymorphism and yield traits ($P<0.05$). The AA genotype exhibited a notable advantage over other genotypes with respect to milk and protein yield ($P<0.05$), and all genotype mean differences were statistically significant for fat yield ($P<0.05$). A subsequent analysis revealed no statistically significant differences between the genotypes concerning fat percentage or protein percentage ($P>0.05$). The results of the meta-analysis indicate that, in the context of marker-assisted selection in the field of dairy cattle breeding, the utilization of AA genotyped individuals can be advantageous in enhancing milk and protein yield.

Keywords: Meta-analysis, FASN, Polymorphism, SMD, Milk production traits

Introduction

In recent years, dairy farmers have increased their focus on milk quality, in addition to milk yield. This shift is driven by the understanding that quality has a direct impact on the selling price within the dairy industry [1]. The enhancement of the genetic quality of dairy cattle through selection constitutes a method employed to improve milk quality [2-4]. Furthermore, single-nucleotide polymorphism (SNP) at the DNA level can be utilized for marker-assisted selection to select superior cattle [5,6]. Milk production is a quantitative trait that is governed by the cumulative additive effect of a limited number of candidate genes. Consequently, genome-wide association studies (GWAS) targeting candidate genes associated with milk production traits are imperative for identifying statistically significant single-nucleotide polymorphisms (SNPs) that may be crucial in marker identification efforts [2,3,6].

SNPs have been utilized in numerous studies to enhance production performance and to understand the genetic background of quantitative traits. Genomic research studies focusing on the identification of markers for bovine milk production parameters have been reported from many parts of the world [2,3,6]. The employment of functional genetic markers has been demonstrated to be a remarkably efficacious strategy across various breeds, enabling precise characterization and evaluation of marker-assisted selection (MAS) methodologies within the framework of the domestic dairy sector. The integration of genomic and quantitative data facilitates the refinement of systems, thereby enhancing production efficiency. The identification of SNPs in candidate genes responsible for milk parameters is of great importance, considering the benefits of genomic selection [7].

The present article engages with the FASN gene, a candidate gene that plays a pivotal role in the synthesis of fatty acids. This gene is situated in a critical linkage region that has been demonstrated to be associated with milk production and the composition of milk fat. FASN gene polymorphisms represent a significant genetic factor influencing milk production and fat composition

in dairy and beef cattle [8-14]. It is a homodimeric enzyme that plays an important role in the general metabolism of animals [15] and during embryonic growth. It also plays a critical role in fat synthesis, especially in adult mammals [16,17]. The expression of the FASN gene in dairy cows has been demonstrated to influence milk fat composition by modulating fatty acid synthesis.

Genomic selection studies related to the FASN gene have been shown to facilitate genetic enhancement by increasing milk fat productivity and enabling genetic improvement, thereby enhancing the economic performance of cattle breeding and milk quality. In cattle, the FASN gene is located in chromosomal regions where there are multiple quantitative trait loci (QTL) affecting traits such as milk fat and fatty acid composition and adipose tissue [18]. The bovine FASN gene is located on the long arm of chromosome 19 (BTA19)-19q22 [19]. The complete sequence of the gene is 19,770 base pairs (bp) in length and contains 42 exons and 41 introns [20].

The A/G polymorphism in exon 34 of the bovine FASN gene is the FASN-16024G>A single-nucleotide substitution, which was identified by Roy et al.[21] in their study as 16009A>G. This significant polymorphism results in an alteration of the THR amino acid for ALA in a region where ketoacyl reductase and enol reductase activity are present. Of the 13 single-nucleotide polymorphisms (SNPs) identified in the FASN gene, two non-synonymous SNPs have been reported to directly relate to lactation parameters in exon 34 [22]. A/G at position 5848 was predicted to result in an amino acid change from threonine to alanine (T1950A), and T/C at position 5863 was predicted to result in an amino acid change from tryptophan to arginine. T1950A genotypes were found to express W1955R genotypes [22,23]. Consequently, it has been asserted that these SNPs are associated with yield traits in Holstein and Japanese Black cattle [24].

Meta-analysis is a statistical methodology designed for the estimation and evaluation of a common effect size, achieved by combining the results of several independent studies on a specific topic. Furthermore, it facilitates a re-evaluation of research findings, enabling the formulation of more robust and reliable conclusions [25]. This approach is employed in instances of duplicate sample size, that is, when independent studies are repeated in response to a comparable research question [26]. In the context of genetic studies targeting livestock, genes that influence traits of economic significance are of particular interest in the identification of genes. In the context of dairy cattle, the focus is on genes that contribute to variation in milk production. In the field of animal husbandry, dairy genes and hormones are regarded as significant genes due to their association with quantitative traits and biological significance [27].

The present meta-analysis was conducted to derive a comprehensive conclusion and consolidate the findings of numerous independent studies on the association between the FASN gene polymorphism and milk production traits in dairy cattle.

Materials and Methods

The Search Strategy for Sources

The selection of articles for the meta-analysis was conducted by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist. A review of the extant literature on the effects of FASN gene polymorphisms and milk production traits (milk yield, fat yield, protein yield, fat content, protein content) in dairy cattle reveals a plethora of studies published in various journals, including Science Direct, Web of Science, PubMed, Taylor & Francis, Google Scholar, Wiley Online Library, ResearchGate, Springer, and NCBI, up to the year 2025. To identify additional studies not included in the previous search, a cross-check was performed on all references in these studies.

Inclusion and Exclusion Criteria

The following criteria have been established to determine inclusion and exclusion:

All authors of the article were conducted independently, and the articles selected for meta-analysis met the following criteria: Polymorphism of the FASN gene and association with milk yield, fat yield, protein yield, fat content, and protein content. The present study exclusively focused on the breeding of cattle of the Bos taurus species. The third item is a sample size, or the number of animals used for each genotype. The fourth point of analysis focuses on the standard deviation and errors associated with the relevant trait, as well as the mean average of that trait for each genotype.

The exclusion criteria were as follows:

-Reports submitted in abstract form.

-Absence of related indicators (e.g., milk yield, fat yield, protein yield, fat content, protein content).

-Summarized and presented publications.

-Absence of a number of cattle for each genotype.

-Inadequate indication of average means and standard deviation/errors per genotype.

-Repeating studies.

Data Extraction

The data was entered into a standard extraction form created in Microsoft Excel 2021 (Microsoft Corp.) to compute the least squares means and standard deviations

(SD) necessary for meta-analysis. A comprehensive review of the extant literature yielded the following information: The following variables were collected for each publication: the year of publication, the country of publication, the first author, the number of cattle, the genotype distribution, the milk yield, the fat yield, the protein yield, the fat content, the protein content, and the mean value and the standard deviation. The following formula was used to convert the standard error (SE) to the standard deviation $(SD = SE\sqrt{N})$.

Statistical Analysis

In the meta-analysis, the fixed effect model was employed for homogeneous data, and the random effect model was used for heterogeneous data, in order to determine the differences between means and proportions. The heterogeneity assumption was calculated based on I^2 with α=0.10 in the heterogeneity analysis. Standard mean differences (SMDs) and standard deviations with 95% confidence intervals (CIs) were calculated to estimate the difference between mean values (α=0.05 was accepted for the effect size test of the traits included). The standardised mean difference (SMD) was calculated using the Cohen method when the number of studies exceeded 10, and the Hedges method when the number of studies was less than 10. The PRISMA flow diagram illustrates the inclusion and exclusion criteria utilized for the selection of studies, with the relevant studies undergoing assessment through a forest plot. The statistical analyses were conducted using Stata 11.2 software (StataCorp 2001; Stata Statistical Software). The significance level was set at α=0.05 for the effect size test of the traits included in the study.

Results

Study Selection

In this study, a total of eighty-nine studies with a theoretical connection were identified through a systematic search of the database and a subsequent screening of the reference list. A total of 89 studies were included in the meta-analysis. However, after the preliminary evaluation, 46 of these studies were identified as duplicates and were thus removed. Following a comprehensive evaluation of the 43 papers, 35 reports were determined to be unsuitable for additional consideration *(Fig. 1)*. The rationale for

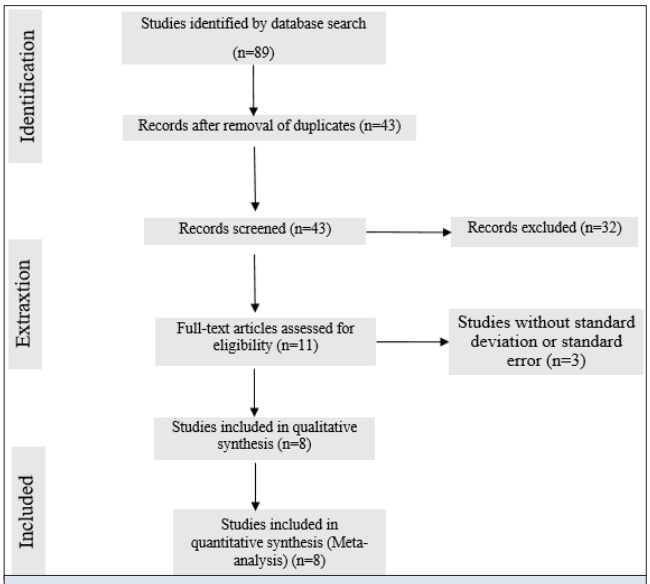

Fig 1. Flow chart summarizing literature search and article selection procedure

Table 1. *Characteristics of studies included in the meta-analysis of FASN gene polymorp-hisms and milk production traits*

Trait	Reference No	Breed	Genotype Frequency			Mean±SD		
			AA	AG	GG	AA	AG	GG
Milk yield	7	Holstein	0	63	37	0±0.0	1247.45±387.34	1189.5±445.26
	11	Simmental	2	15	32	6462.95±1294.01	5773.65±1535.64	5627.25±1483.79
	11	Crossbred Holstein	0	9	25	0± 0.0	6850.3±1390.8	6048.15±1570.75
	22	Holstein	0	58	137	0±0.0	11864.5±3577.13	11672.35±2498.95
	29	Simmental	1	20	51	8352.0±0.0	7430.95±1138.09	7404.86±1073.26
	29	Hols×Sim	0	9	24	0±0.0	7794.48±835.8	7501.45±1100.22
	30	Holstein	73	14	4	8080.82±2787.91	7812.57±1220.9	6995.75±652.6
	31	Holstein and Simmental	0	378	1018	0±0.0	8527.0±3071.87	8277.0±3094.89
	32	Holstein (1)[&]	12	57	40	9060.0±1118.9	8187.0±1509.97	8708.0±1650.71
	32	Holstein (2)	12	57	40	12566.0±1895.01	11018.0±2017.53	11386.0±2042.83
	32	Holstein (3)	12	57	40	12599.0±1389.1	11919.0±1864.81	12191.0±2042.83

Table 1. *Characteristics of studies included in the meta-analysis of FASN gene polymorp-hisms and milk production traits (continued)*

Trait	Reference No	Breed	Genotype Frequency			Mean±SD		
			AA	AG	GG	AA	AG	GG
Fat yield	7	Holstein	0	63	37	0±0.0	168.61±58.5	158.71±54.01
	29	Simmental	1	20	51	305±0.0	296.24±40.2	304.22±48.71
	29	Hols×Sim	0	9	24	0±0.0	347.33±46.95	308.85±53.47
	31	Holstein and Simmental	0	378	1018	0±0.0	349.8±124.43	339.6±124.43
	32	Holstein (1) &	12	57	40	387±51.96	351.0±67.95	363.0±56.92
	32	Holstein (2)	12	57	40	517±41.57	471.0±90.6	463.0±82.22
	32	Holstein (3)	12	57	40	491±48.5	489.0±90.6	480.0±88.54
Fat content	7	Holstein	0	63	37	0±0.0	4.05±0.71	4.22±0.61
	11	Simmental	2	15	32	3.43±0.72	3.93±0.85	3.99±0.85
	11	Crossbred Holstein	0	9	25	0±0.0	4.68±0.78	3.98±0.9
	22	Holstein	0	58	137	0 ± 0.0	3.77±1.14	3.87±0.06
	29	Simmental	1	20	51	3.65±0.0	4.01±0.4	4.11±0.43
	29	Hols×Sim	0	9	24	0±0.0	4.47±0.54	4.12±0.43
	30	Holstein	73	14	4	3.68±0.26	3.69±0.11	3.87±0.07
	31	Holstein and Simmental	0	378	1018	0±0.0	4.13±0.39	4.11±0.32
	32	Holstein (1) &	12	57	40	4.28±0.28	4.31±0.45	4.22±0.57
	32	Holstein (2)	12	57	40	4.42±0.42	4.29±0.45	4.12±0.57
	32	Holstein (3)	12	57	40	3.93±0.52	4.12±0.6	3.97±0.6
	33	Holstein × Friesian	26	19	0	2.48±0.18	2.79±0.21	0.0±0.0
Protein yield	7	Holstein	0	63	37	0±0.0	118.35±37.46	115.54±41.73
	29	Simmental	1	20	51	270±0.0	254.54±33.93	258.22±36.1
	29	Hols×Sim	0	9	24	0±0.0	282.13±22.07	268.41±35.39
	31	Holstein and Simmental	0	378	1018	0±0.0	290.5±95.27	285.4±95.72
	32	Holstein (1) &	12	57	40	306±34.64	279.0±45.3	290.0±44.27
	32	Holstein (2)	12	57	40	416±48.5	364.0±60.4	373.0±56.92
	32	Holstein (3)	12	57	40	413±45.03	388.0±60.4	387.0±56.92
Protein content	7	Holstein	0	63	37	0.0±0.0	2.9±0.24	3.08±0.18
	11	Simmental	2	15	32	3.49±0.37	3.61±0.43	3.64±0.4
	11	Crossbred Holstein	0	9	25	0.0±0.0	3.83±0.39	3.79±0.45
	22	Holstein	0	58	137	0.0±0.0	3.33±0.38	3.27±0.23
	29	Simmental	1	20	51	3.23±0.0	3.44±0.24	3.49±0.19
	29	Hols×Sim	0	9	24	0.0±0.0	3.63±0.2	3.59±0.24
	30	Holstein	73	14	4	3.08±0.26	3.07±0.04	3.1±0.02
	31	Holstein and Simmental	0	378	1018	0.0±0.0	3.43±0.39	3.48±0.32
	32	Holstein (1) &	12	57	40	3.39±0.17	3.41±0.15	3.35±0.19
	32	Holstein (2)	12	57	40	3.42±0.24	3.3±0.15	3.33±0.19
	32	Holstein (3)	12	57	40	3.28±0.17	3.26±0.23	3.19±0.19

SD: standard deviation, & (1,2,3): Lactation period

exclusion is outlined below: The present study was not designed to investigate the association between FASN gene polymorphisms and fatty acid traits in muscle. Furthermore, the data provided was inadequate for the objectives of the study. The study revealed a paucity of essential information, including genotype frequencies, standard deviation, and the necessary single-nucleotide polymorphisms (SNPs). The emphasis was placed on other traits, rather than on milk yield.

Table 1 provides information about the studies that are the focus of the research. It presents the means and standard deviations of the phenotypic characteristics of the examined breeds and genotypes in each study.

Association Analysis

The present study incorporated a total of five performance traits derived from eight articles. To facilitate a more profound comprehension of the subject, the collective results of the meta-analysis were illustrated in the forest plot displayed in *Fig. 2*, *Fig. 3*, *Fig. 4*, *Fig. 5*, and *Fig. 6*. The study presented the significant results of a systematic review and meta-analysis of FASN gene polymorphisms and their association with milk production traits (milk yield, fat yield, fat content, protein yield, and protein content) in dairy cattle.

In the context of association analysis, forest plots derived from these meta-analyses facilitate enhanced comprehension of the outcomes. These plots offer a visual representation of the means of the compared groups, the position of the overall mean differences across all studies, and the position of the mean differences of each study in the forest plots. To interpret the results of the meta-analysis, the black squares in the Forest plot graph represent the standard mean difference for the relevant feature, and the horizontal lines represent the 95% confidence interval. The results of the meta-analysis demonstrated a significant discrepancy between the comparison groups (P<0.05). This discrepancy was indicated by the presence of a diamond shape and a vertical dashed line, as well as by the presence of a continuous line when the confidence interval of the effect size was not altered. A similar evaluation was made within the confidence interval line of each study: If the confidence interval intersected with the vertical line, the difference was deemed to be non-statistically significant (P>0.05). Conversely, if the confidence interval did not intersect with the vertical line, the difference was considered to be statistically significant (P<0.05).

The analysis encompassed a total of five performance traits derived from eight studies, with each genotype subjected to separate analysis within the framework of co-dominant models. The results of this analysis are presented in *Table 2*. Furthermore, the results of the meta-analysis of the differences between allelic groups of the examined yield traits are presented in *Table 2* and *Fig. 2*, *Fig. 3*, *Fig. 4*, *Fig. 5*.

The random effect model was applied due to the heterogeneity regarding fat content exhibited by the AA-AG and AG-GG genotypes, and protein content exhibited by the AG-GG genotype. The fixed effect model was employed for other traits because they were found to be homogeneous.

Table 2. *Meta-analysis results of the associations between FASN gene polymorphisms and milk production traits*

Traits		N	SMD	95%CI	I^2	Model	P-Value (Meta-analysis)
AA vs AG	Milk yield	5	0.45	0.15;0.75	0.0	F	**0.003****
	Fat yield	3	0.37	0.00;0.73	0.0	F	**0.048***
	Fat content	6	-0.46	-0.94;0.02	**64.7**	R	0.060
	Protein yield	3	0.63	0.27;1.00	0.0	F	**0.001****
	Protein content	6	0.04	-0.26;0.34	0.0	F	0.798
AA vs GG	Milk yield	5	0.36	0.02;0.70	0.0	F	**0.040***
	Fat yield	3	0.42	0.04;0.79	0.0	F	**0.030***
	Fat content	5	-0.09	-0.43;0.25	0.0	F	0.610
	Protein yield	3	0.53	0.16;0.91	0.0	F	**0.006****
	Protein content	5	0.18	-0.16;0.52	0.0	F	0.291
AG vs GG	Milk yield	11	0.05	-0.04;0.14	0.0	F	0.309
	Fat yield	7	0.07	-0.03;0.17	0.0	F	0.144
	Fat content	11	0.02	-0.20;0.24	**67.0**	R	0.831
	Protein yield	7	0.02	-0.07;0.12	0.0	F	0.659
	Protein content	11	-0.04	-0.25;0.17	**64.0**	R	0.728

**P<0.05; **P<0.01; F: Fixed; R: Random; n: number of publications; Variation in SMD attributable to heterogeneity*

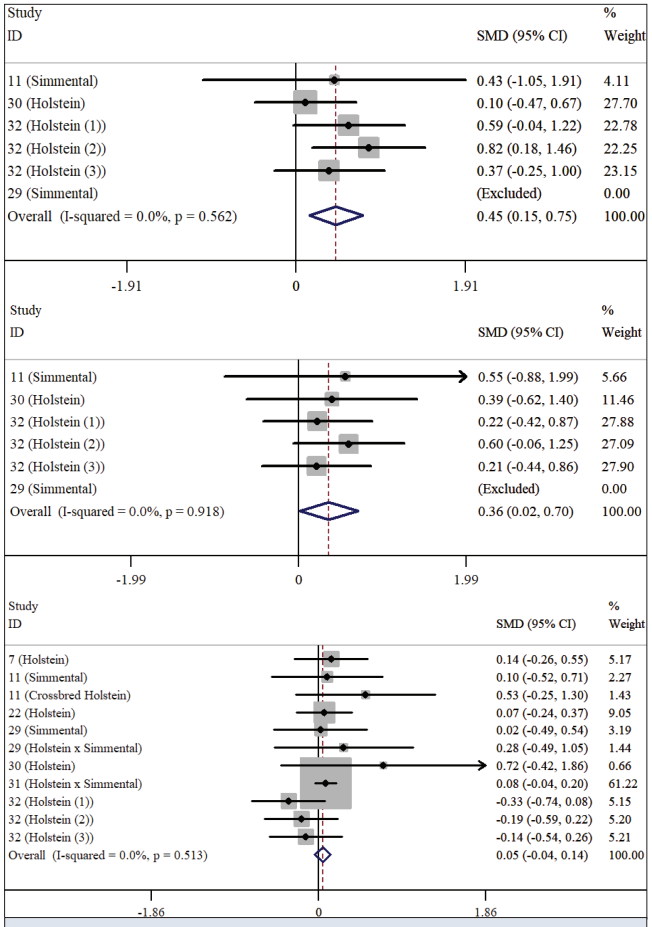

Fig 2. Forest plots of the studies examining the effect of *FASN* gene polymorphism on milk yield trait (Co-dominant model, from top to bottom; AA-AG, AA-GG, AG-GG, respectively)

The weight of the studies is represented by a square in each of the figures below. The horizontal line in the graph indicates the confidence interval for each study, with the overall result represented by a diamond at the bottom of the graph.

A subsequent meta-analysis of the available literature yielded results that were statistically significant (P<0.05) for the association between AA-AG, AA-GG, and milk yield, while AG-GG indicated non-significant (P>0.05) results *(Fig. 2)*. In a similar vein, the polymorphisms of the FASN gene with fat yield were found to be statistically significant (P<0.05), with the AA-AG and AA-GG polymorphisms demonstrating a statistically significant association with fat yield, and the AG-GG polymorphism indicating a non-significant association (P>0.05) *(Fig. 3)*. However, the relationship between fat content and the AA-AG, AA-GG, and AG-GG genotypes was found to be insignificant (P>0.05) *(Fig. 4)*. As demonstrated in Figure 5, the mean differences in protein yield for AA-AG and AA-GG genotypes were found to be statistically significant (P<0.01). However, no statistically significant differences were observed between AG-AG genotypes (P>0.05). In

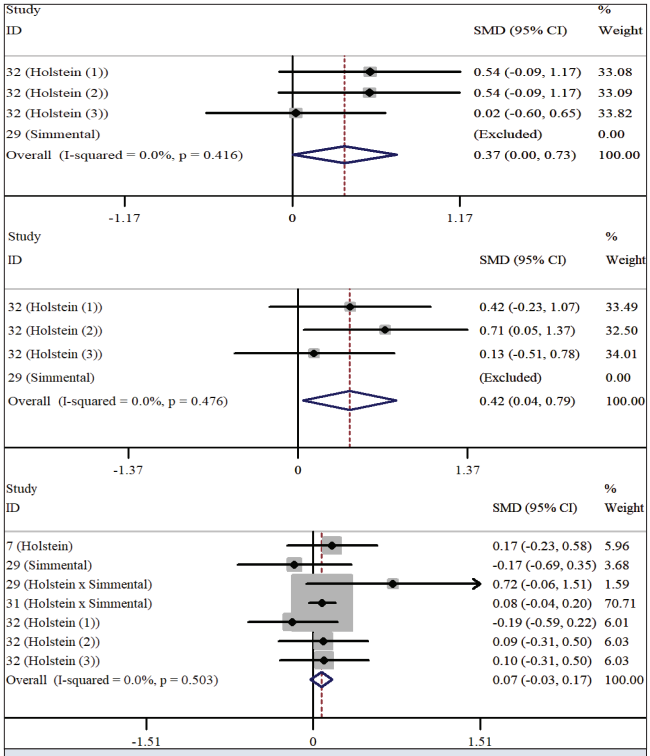

Fig 3. Forest plots of the studies examining the effect of *FASN* gene polymorphism on fat yield trait (Co-dominant model, from top to bottom; AA-AG, AA-GG, AG-GG, respectively)

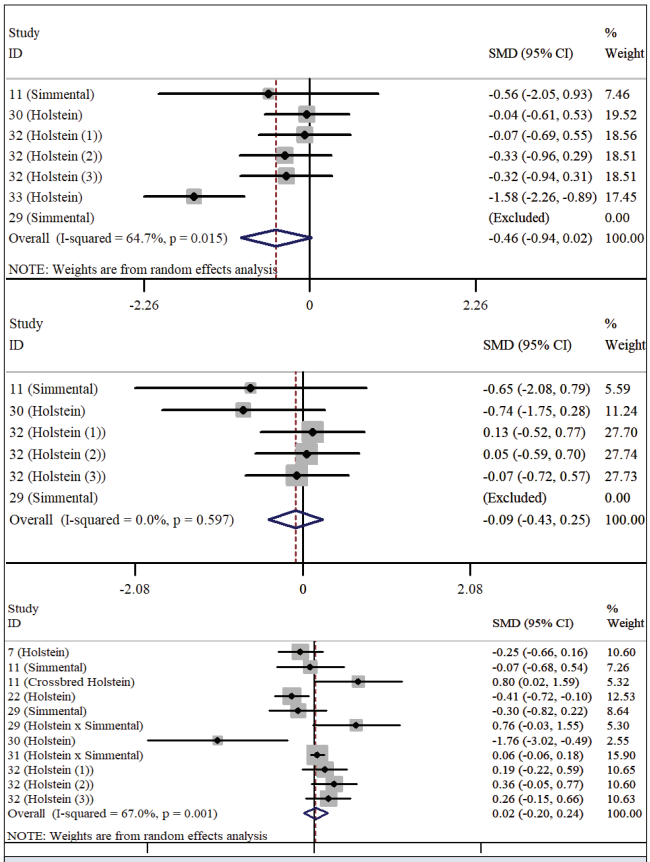

Fig 4. Forest plots of the studies examining the effect of *FASN* gene polymorphism on fat content (Co-dominant model, from top to bottom; AA-AG, AA-GG, AG-GG, respectively)

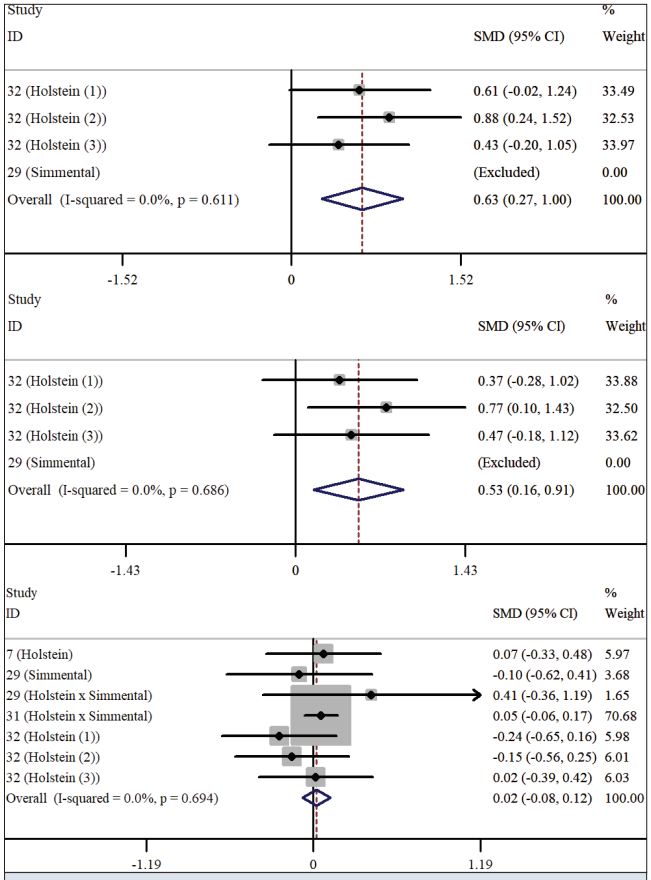

Fig 5. Forest plots of the studies examining the effect of FASN gene polymorphism on protein yield trait (Co-dominant model, from top to bottom; AA-AG, AA-GG, AG-GG, respectively)

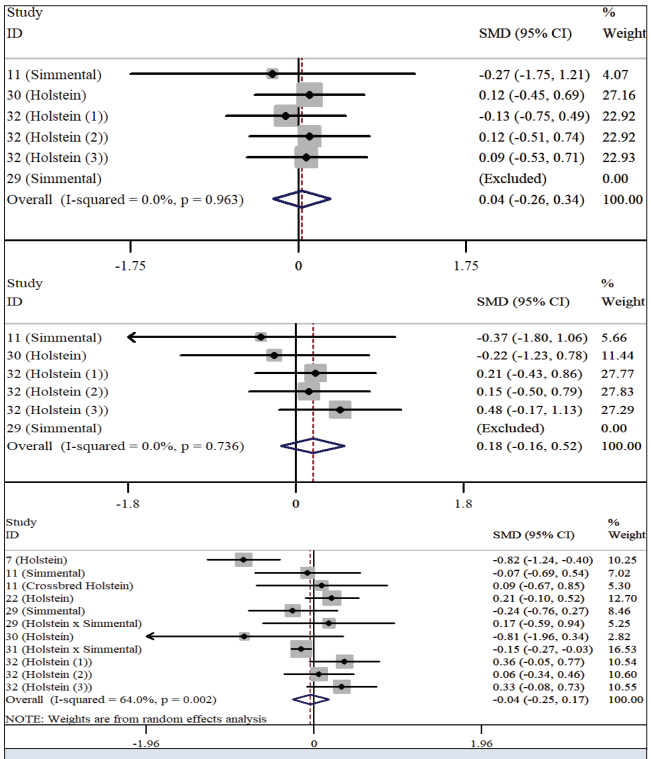

Fig 6. Forest plots of the studies examining the effect of FASN gene polymorphism on fat content (Co-dominant model, from top to bottom; AA-AG, AA-GG, AG-GG, respectively)

the protein content analysis, the mean differences of all genotypes were not significant (P>0.05) (*Fig. 6*).

Discussion

Regarding the milk yield trait, the P values of the studies incorporating FASN gene polymorphism are predominantly above the significance level, indicating that no statistically significant relationship was observed (P>0.05) [22,28-32]. In a particular study, the relationship between milk yield and FASN gene polymorphism was examined, and it was found to have a significant effect on polymorphism (P<0.05) [28]. Among the five studies that examined the relationship between FASN gene polymorphism and fat yield, a significant difference (P<0.05) was identified in the Ciecierska et al., 2013 study; however, no significant difference was found in the other studies (P>0.05) [7,27,31,32]. Among the nine studies that examined the relationship between fat content and FASN gene polymorphism, Matsumoto et al.[22] and Mauric et al.[28] reported a significant difference (P<0.05). However, no significant difference was found in other studies (P>0.05) [7,28,29,31-33]. A single study has identified a significant relationship (P<0.05) between protein yield and FASN gene polymorphism [15], while the remaining studies have not detected a significant difference (P>0.05) [7,29,31,32]. The majority of studies examining the relationship between FASN gene polymorphisms and protein content found no significant relationship (P>0.05) [21,27-30], but four studies found a significant relationship (P<0.05) [7,28,29,31].

The results of the meta-analysis conducted in this study indicate a significant association between the FASN gene polymorphism and milk, fat, and protein yields. The results indicate that the genotype comparisons that demonstrated a significant relationship with milk, protein, and fat yield were AA-GG and AA-AG, while the genotypes that did not demonstrate a significant relationship were determined as AG-GG. No significant correlation was identified between the protein and fat content and the FASN genotypes. A meta-analysis of the extant literature yielded a finding that was consistent across studies: individuals carrying the AA genotype exhibited higher yields of milk, fat, and protein. This finding suggests that the FASN locus is an important candidate gene for marker-assisted selection.

Conclusion

In this learning study, it was observed that the FASN gene was effective on milk components. It has been posited that this particular gene warrants consideration, particularly in the context of selection applications focused on fat, protein, and milk yield. An analysis of the fat and protein content characteristics revealed no

statistically significant differences. Consequently, it is hypothesized that these traits may be more influenced by other environmental and genetic factors. Future studies should include genotype × environment interactions. The utilization of substantial data sets is instrumental in enhancing reliability and attaining more generalizable outcomes. The study suggested the inclusion of FASN gene polymorphisms in cattle breeding programs and thus demonstrated its potential application as a genetic marker to enhance milk production efficiency. It is hypothesized that further consideration of the FASN gene may result in enhanced milk yield and quality.

Declarations

Availability of Data and Materials: The data and materials of this study are available from the corresponding author (M. Özdemir).

Competing Interests: The authors declared that there is no competing interest.

Artificial Intelligence: AI and AI-assisted technologies have not been used during the writing process of this study.

Author Contributions: Idea/Concept: DG, IA, ES; Design: MO, DG, IA, ES; Data Collection and/or Processing: DG, IA, ES; Analysis and/or Interpretation: MO, DG; Writing of the Manuscript: MO, DG, IA, ES; Critical Review: MO.

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