Kafkas Universitesi Veteriner Fakultesi Dergisi
Journal Home-Page: http://vetdergikafkas.org
ISSN: 1309-2251

Kafkas Univ Vet Fak Derg
28 (5): 613-620, 2022
DOI: 10.9775/kvfd.2022.27770

RESEARCH ARTICLE

Associations Between c.2832A > G Polymorphism of *CAST* Gene and Meat Tenderness in Cattle: A Meta-Analysis

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Article ID: KVFD-2022-27770 Received: 15.05.2022 Accepted: 14.08.2022 Published Online: 15.08.2022

Abstract: Genes or genetic markers related to meat quality have been studied for many years. The *CAST* gene is one candidate gene affecting meat tenderness in cattle. This meta-analysis aimed to examine the association of c.2832A>G polymorphism of the *CAST* gene and meat tenderness in cattle. According to the determined criteria, 17 studies were included in the meta-analysis, and pooled ratios of allele and genotype frequencies were calculated. In addition, the combined Warner-Braztler Shear Force values were calculated for three studies that reported these values according to genotypes for the meat tenderness feature. Heterogeneity between studies and publication bias were also tested. As a result of the meta-analysis, pooled ratios of AA, AG, and GG genotypes are 0.578, 0.342, and 0.080; pooled ratios of A and G alleles are 0.777 and 0.223. The highest pooled ratios were obtained for AA genotype and A allele. The combined Warner-Braztler shear force values were calculated as 3.707, 3.893, and 5.137 kilogram-force for AA, AG, and GG genotypes. The highest mean shear force value was obtained for the GG genotype. In conclusion, the meta-analysis results examined the relationship between c.2832A>G polymorphism of the *CAST* gene and meat tenderness were closer to the population parameter. This study may improve genetic selection and provide new strategies to increase meat quality in cattle.

Keywords: *CAST gene, Cattle, Meta-analysis, Meat tenderness, Polymorphism*

CAST Geninin c.2832A > G Polimorfizmi ile Sığırlarda Et Gevrekliği Arasındaki İlişki: Bir Meta-Analizi

Öz: Et kalitesiyle ilgili genler veya genetic belirteçler uzun yıllardır araştırılmaktadır. *CAST* geni, sığırlarda et gevrekliğini etkileyen bir aday gendir. Bu meta analizi, sığırlarda *CAST* geninin c.2832A>G polimorfizmi ile et gevrekliği arasındaki ilişkiyi incelemeyi amaçlamıştır. Belirlenen kriterlere göre, 17 çalışma meta analize dahil edilmiş ve allel ve genotip frekansların birleştirilmiş oranları hesaplanmıştır. Bunun yanında, etin gevreklik özelliği için Warner-Braztler kesme kuvveti değerlerini genotiplere göre veren üç çalışmanın sonucu için birleştirilmiş kesme kuvveti değeri hesaplanmıştır. Çalışmalar arası heterojenlik ve yayın yanlılığı da test edilmiştir. Meta-analizi sonucunda AA, AG ve GG genotiplerinin birleştirilmiş oranları 0.578, 0.342 ve 0.080; A ve G alellerinin birleştirilmiş oranları 0.777 ve 0.223 olarak elde edilmiştir. En yüksek birleştirilmiş oranlar AA genotipi ve A alleli için elde edilmiştir. Birleştirilmiş Warner-Braztler kesme kuvveti değerleri AA, AG ve GG genotipleri için sırasıyla 3.707, 3.893 ve 5.137 kilogram kuvvet olarak hesaplanmıştır. En yüksek ortalama kesme kuvveti değeri GG genotipi için elde edilmiştir. Sonuç olarak, *CAST* geninin c.2832A>G polimorfizmi ile et gevrekliği arasındaki ilişkinin incelendiği meta-analiz sonuçları populasyon parametresine yakın bulunmuştur. Bu çalışma sığırlarda genetik seçimi geliştirmek ve et kalitesini arttırmak için yeni stratejiler sağlayabilir.

Anahtar sözcükler: *CAST geni, Et gevrekliği, Meta-analiz, Polimorfizm, Sığır*

INTRODUCTION

Meat tenderness is one of the characteristics that determine meat quality, and it is an essential factor affecting the satisfaction in beef consumption. Two enzymes are responsible for the meat tenderness property used to improve genetic selection: *calpain (CAPN1)* and its inhibitor, calpastatin (*CAST*) genes [1]. The *CAPN1* gene, which degrades postmortem myofibrillar proteins, is located on bovine chromosome 29. The *CAST* gene is

How to cite this article?
Uzabaci E, Dincel D: Associations between c.2832A > G polymorphism of *CAST* gene and meat tenderness in cattle: A meta-analysis. *Kafkas Univ Vet Fak Derg,* 28 (5): 613-620, 2022.
DOI: 10.9775/kvfd.2022.27770

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located on BTA 7 [2,3]. Several markers have been developed in the *CAST* gene and three in the *CAPN1* gene [4,5]. These markers were independently examined in previous studies and have been suggested as being associated with meat tenderness in beef cattle [1,4,5].

Especially several variants of the *CAST* gene have been reported in studies conducted on different breeds of cattle [6-8]. Some of these studies examined the association between c.2832A>G polymorphism of the *CAST* gene and meat tenderness. Different results were obtained due to sample sizes [7,9,10]. To address this problem about differences, large sample sizes or meta-analysis are required to determine the genetic effects of the c.2832A>G polymorphism on meat tenderness in cattle.

Systematic reviews and meta-analysis studies combine the findings from different studies on the same subject and evaluate them using statistical methods. Accordingly, the statistical power and precision of estimating an SNP effect on a trait in individual studies with small sample sizes can be increased with meta-analysis studies that have also become widespread in genetics. Even though the previous meta-analyses had discussed the association between different gene variants and milk yield in cattle [11-13], this study examines the relationship between the related gene and meat tenderness.

This study aimed to evaluate the genotype and allele frequencies of c.2832A>G polymorphism of the bovine *CAST* gene with meta-analysis. In addition, it was aimed to examine the relationship of this SNP with meat tenderness in cattle.

MATERIAL AND METHODS

Ethical Statement

This study was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist criteria [14]. The data for this research were collected from online databases, so this study does not require any ethical permission.

Literature Search Strategy

A comprehensive literature search was conducted through PubMed and Web of Science databases in January 2022 using the keywords "*calpastatin* gene" and "cattle" to detect relevant studies.

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (a) studies providing genotype and/or allele frequencies and sample sizes of *CAST* gene c.2832A>G polymorphism in cattle; (b) the full text can be obtained; (c) published in English or Turkish language. All relevant reports were screened first by title and then full-text to avoid duplication. Exclusion criteria are (a) about other *CAST* gene polymorphisms; (b) duplicated data; (c) abstract, review, and case reports; (d) provided insufficient data; (e) other species experiments. In addition, for subgroup analysis to examine the relationship between the *CAST* gene c.2832A>G polymorphism and meat tenderness, studies reporting the Warner-Braztler Shear Force (WBSF) values according to genotypes (AA, AG, and GG) were included.

Data Extraction

All authors independently screened all selected studies in full text to determine whether they met the inclusion and exclusion criteria. A standard data extraction form was used to extract the following data: first author's name, publication year, region, cattle breed, sample size, genotype (AA, AG, and GG), and allele (A and G) gene frequencies. In some studies, the frequencies of the genotypes were not given separately. In this case, only allele frequencies were included in those studies. In addition, in some studies, the frequencies were obtained by calculating ratios, while in some studies, the genotype frequencies were calculated manually. Since some studies used more than one breed and frequencies were specified for each breed in detail, each breed was taken as a separate study. Any disagreement was resolved by discussion between the authors. For subgroup analysis to examine the relationship between the *CAST* gene c.2832A>G polymorphism and meat tenderness, least-square means (with standard error) of WBSF values according to genotypes were extracted. When the standard error of the mean was reported, it was converted to standard deviation.

Statistical Analysis

Before meta-analysis, publication bias was evaluated quantitatively with Begg's adjusted rank correlation test and graphically with funnel plots. The heterogeneity of effect sizes between studies was assessed with the Cochran Q test. Q statistics and I^2 statistics were calculated. I^2 values higher than 50% were considered as high heterogeneity. Based on the heterogeneity test results, the fixed-effect model was used when heterogeneity was low; otherwise, a random effect model was employed to compute pooled effect sizes. In this study, pooled ratios were calculated with 95% confidence intervals concerning all the genotypes (AA, AG, and GG) and allele (A and G) frequencies. In evaluating genotype and allele frequencies, studies were classified according to cattle breeds as *Bos taurus*, *Bos indicus*, and cross breed. Analyzes were performed separately for both breed type and total. In addition, point estimates of WBSF values were calculated for each genotype separately (Hedges method). In the evaluation of heterogeneity and publication bias, $\alpha=0.10$ was taken. R software (version 4.1.2) was utilized to perform a meta-analysis in this study.

RESULTS

Study Characteristics

The study selection process is shown in *Fig. 1*. A total of 228 articles were retrieved. According to the inclusion and exclusion criteria, the final selected articles were 17 and were published from 2006 to 2021. The characteristics of the selected studies and frequency distribution of genotype and allele gene were presented in *Table 1*. Since frequency values of more than one cattle breed were reported in some studies, each result was considered as a separate trial result. For this reason, the relevant table includes 26 trial results from 17 publications. The findings of 21 trials reporting genotype frequencies (AA, AG, and GG) and 26 trials containing allele frequencies (A and G) were given in this table. Among the identified studies, the relationship between meat tenderness and c.2832A>G polymorphism of bovine *CAST* gene was examined, and Warner-Braztler Shear Force (WBSF) values were entirely reported in three studies. WBSF values of these studies according to genotypes were given in *Table 2*.

Meta-analysis Results

All meta-analysis results applied to combine the genotype and allele frequencies are represented in *Table 3*. Cochran's Q and I^2 test statistics were reported with p values in the relevant table.

Considering all the studies, according to calculated I^2(%) and P values, statistically significant (P<0.001) and high heterogeneity was detected in all genotypes and alleles. Therefore, the pooled ratios were obtained with the random effect model. As a result of the meta-analysis, the AA genotype pooled ratio of 0.578 (0.485-0.666) was calculated higher than AG and GG genotypes, and the A allele pooled ratio of 0.777 (0.725-0.822) was calculated higher than the G allele. Forest plots related to the meta-analysis of genotypes and alleles for all studies were represented in *Fig. 2*. As a result of Begg's test, it was determined that there was no publication bias for all genotypes and alleles. Funnel plots represented in *Fig. 3* also showed no evidence of publication bias.

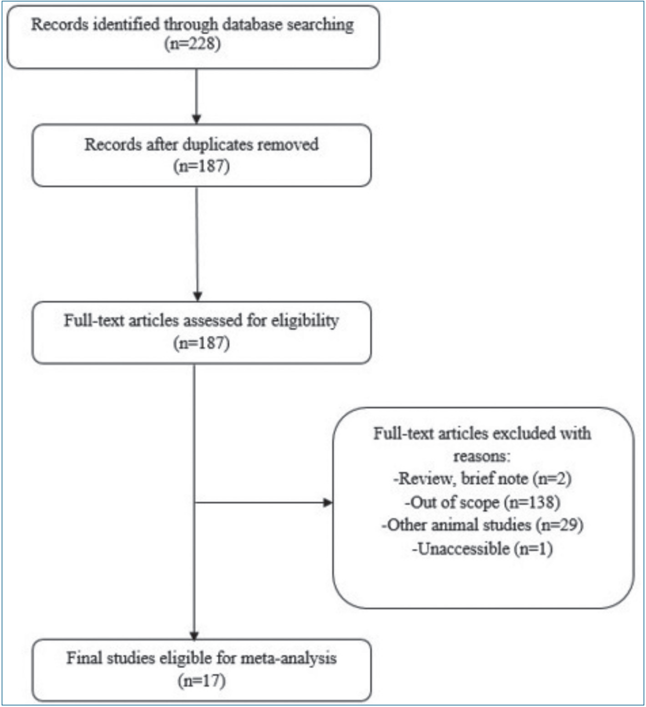

Fig 1. Flowchart of study selection for meta-analysis

According to meta-analysis results for *Bos taurus* breed, calculated I^2(%) and p values show that there is statistically significant (P<0.001) and high heterogeneity in all genotypes and alleles. Therefore, the pooled ratios were obtained with the random effect model. The AA genotype pooled ratio of 0.626 (0.512-0.727) was calculated higher than AG and GG genotypes, and the A allele pooled ratio of 0.798 (0.742-0.845) was calculated higher than the G allele. Also, it was determined that there was no publication bias for all genotypes and alleles with Begg's test.

The meta-analysis results of the *Bos indicus* breed for AA genotype (Q=23.41, P<0.001, I^2=87.2%) and AG genotype (Q=13.12, P=0.004, I^2=77.1%) show that heterogeneity is statistically significant and high. For the GG genotype, the heterogeneity between studies is not significant (P=0.542), and a fixed-effect model was used to calculate the pooled ratio. For A and G alleles, statistically significant and high heterogeneity (Q= 9.36, I^2=67.9%, P=0.025) was detected. For studies including *Bos indicus* breed cattle, the AG genotype pooled ratio was calculated higher than AA and GG genotypes. The A allele pooled ratio was higher than the G allele.

According to meta-analysis results for the cross breed of *Bos indicus* and *Bos taurus*, calculated I^2(%) and p values show statistically significant and high heterogeneity in only the AA genotype (Q=13.02, P=0.023, I^2=61.6%). The random-effects model was used to calculate the effect size for the AA genotype, and the fixed effect model was used for other genotypes and alleles. For studies including cross breeds, the AA genotype pooled ratio was calculated higher than AG and GG genotypes, and the A allele pooled ratio was higher than the G allele. The Begg's test could not be performed because less than ten studies were included in the meta-analysis for *Bos indicus* and cross breed groups.

To examine the association between c.2832A>G polymorphism of the *CAST* gene and meat tenderness, three studies with sufficient data were combined with a meta-analysis. All results are represented in *Table 4*. High heterogeneity was determined (I^2=71.40%, *P*=0.030) for the AA genotype, and pooled mean of WBSF value in

***Table 1.** Basic characteristics, genotype, and allele frequency distribution of studies included in the meta-analysis*

No	Study	Year	Country	Breed	n	Genotype Frequency (*n*)			Allele Frequency (n)	
						AA	AG	GG	A	G
1	Allais et al.[6]	2011	France	Blonde d'Aquitaine	971	568	358	45	747	224
2	Allais et al. [6]	2011	France	Charolais	1094	738	321	35	899	195
3	Allais et al.[6]	2011	France	Limousin	1245	838	384	23	1030	215
4	Barendse et al.[9]	2007	Australia	Brahman, Angus, Belmont Red	4936	-	-	-	3899	1037
5	Cafe et al. [7]	2010	Australia	Brahman	143	51	51	41	77	66
6	Casas et al.[1]	2006	USA	MARCIII population^{+}	539	349	166	24	432	107
7	Casas et al.[15]	2013	USA	Hereford, Angus, Red Poll crosses	248	-	-	-	206	42
8	Castro et al.[16]	2016	Colombia	Braunvieh, Limousin, Normande	85	-	-	-	60	25
9	Curi et al.[10]	2009	Brazil	Nelore	114	39	49	26	64	50
10	Curi et al.[10]	2009	Brazil	Angus x Nelore	67	53	14	0	60	7
11	Curi et al.[10]	2009	Brazil	Rubia Gallega x Nelore	44	29	15	0	37	7
12	Curi et al.[10]	2009	Brazil	Canchim	41	20	17	4	29	12
13	Curi et al.[10]	2009	Brazil	Brangus three-way crosses^{++}	19	13	6	0	16	3
14	Curi et al.[10]	2009	Brazil	Braunvieh three-way crosses^{+++}	15	7	8	0	11	4
15	Cushman et al.[17]	2021	USA	MARCIII population	187	58	97	32	107	80
16	Frylinck et al.[18]	2009	South Africa	Brahman	19	11	8	0	15	4
17	Frylinck et al.[18]	2009	South Africa	Simmental	20	16	4	0	18	2
18	Frylinck et al.[18]	2009	South Africa	Nguni	19	14	5	0	17	2
19	Gruber et al.[19]	2011	USA	Charolais-Angus crosses	343	261	82	0	302	41
20	Johnston and Graser [20]	2010	Australia	Angus, Hereford, Murray Grey, Shorthorn	3136	-	-	-	2741	395
21	Li et al.[21]	2010	South Korea	Chinese cattle breeds	212	112	73	27	149	63
22	Morris et al.[22]	2016	New Zealand	Jersey-Limousin, Angus and Hereford-crosses	746	664	75	7	702	44
23	Pintos and Corva [8]	2011	Argentina	Argentinian Angus	268	-	-	-	211	57
24	Tait et al.[23]	2014a	USA	MARCIII population^{+}	199	95	82	22	136	63
25	Tait et al.[24]	2014b	USA	MARCIII population^{+}	254	101	128	25	165	89
26	Tizioto et al.[25]	2014	Brazil	Nelore	178	30	99	49	80	98
Total					15142	4067	2042	360	12210	2932

$^{+}$ MARCIII: (composite of ¼ Hereford, ¼ Angus, ¼ Pinzgauer, and ¼ Red Poll), $^{++}$ (9/16 B. Taurus + 7/16 B. indicus), $^{+++}$ (3/4 B. Taurus + 1/4 B. indicus)

***Table 2.** The Warner-Braztler Shear Force (WBSF) values according to the CAST - c.2832A >G genotypes*

No	Study	Year	AA		AG		GG	
			n	LSM±SE	n	LSM±SE	n	LSM±SE
1	Cafe et al.[7]	2010	51	4.74±1.93	51	4.98±1.93	41	5.54±1.93
2	Curi et al.[10]	2009	39	3.46±0.07	49	3.88±0.07	26	-
3	Li et al.[21]	2010	112	3.98±0.19	73	4.01±0.22	27	5.13±0.28

** Values of shear force presented as least square mean ± standard error (LSM±SE) (in kgf unit); **LSM:** Least square mean*

the studies was calculated with a random effect model as 3.707 (3.210-4.203) kgf. Heterogeneity was not significant for AG and GG genotypes (I^2=0.00%). Therefore, the fixed-effect model was chosen, and pooled mean of WBSF values was calculated as 3.893 (3.762-4.024) kgf and 5.137 (4.594-5.679) kgf for AG and GG genotypes, respectively. The highest mean shear force value was obtained for the GG genotype. Begg's test could not be applied because the combined studies were less than 10.

Discussion

In this study, 17 out of 228 publications retrieved from Pubmed and Web of Science were suitable for meta-analysis. Firstly, genotype and allele frequencies obtained from studies examining the c.2832A>G polymorphism of the bovine CAST gene were combined with a meta-analysis. This step combined 21 frequency values for AA, AG and GG genotypes and 26 frequency values for

Table 3. *Evaluation results of genotype and allele frequencies of CAST gene with meta-analysis method*

Cattle Breed	Genotype/Allele		Number of Trials	Pooled Ratio	95% CI	Heterogeneity			Publication Bias
						Cochran Q	P Value	I^2 (%)	P Value*
Bos taurus	Genotype	AA	11	0.626	0.512-0.727	384.08	<0.001	97.4	0.139
		AG	11	0.316	0.243-0.399	243.83	<0.001	95.9	0.585
		GG	11	0.058	0.029-0.094	146.71	<0.001	94.5	0.697
	Allel	A	15	0.798	0.742-0.845	321.28	<0.001	95.6	0.804
		G	15	0.202	0.155-0.258	321.28	<0.001	95.6	0.804
Bos indicus	Genotype	AA	4	0.327	0.209-0.472	23.41	<0.001	87.2	-
		AG	4	0.433	0.361-0.534	13.12	0.004	77.1	-
		GG	4	0.240	0.227-0.310	1.23	0.542	0.0	-
	Allel	A	4	0.538	0.453-0.620	9.36	0.025	67.9	-
		G	4	0.462	0.380-0.547	9.36	0.025	67.9	-
Cross breed	Genotype	AA	6	0.653	0.544-0.749	13.02	0.023	61.6	-
		AG	6	0.317	0.257-0.384	8.65	0.124	42.2	-
		GG	6	0.030	0.007-0.050	13.20	1.000	0.0	-
	Allel	A	7	0.791	0.780-0.802	8.36	0.213	28.2	-
		G	7	0.209	0.198-0.220	8.36	0.213	28.2	-
Total	Genotype	AA	21	0.578	0.485-0.666	587.96	<0.001	96.6	0.717
		AG	21	0.342	0.288-0.401	300.70	<0.001	93.3	0.952
		GG	21	0.080	0.046-0.141	340.50	<0.001	96.5	0.393
	Allel	A	26	0.777	0.725-0.822	549.11	<0.001	95.4	0.774
		G	26	0.223	0.178-0.275	549.11	<0.001	95.4	0.774

** Begg and Mazumdar Rank Correlation Test*

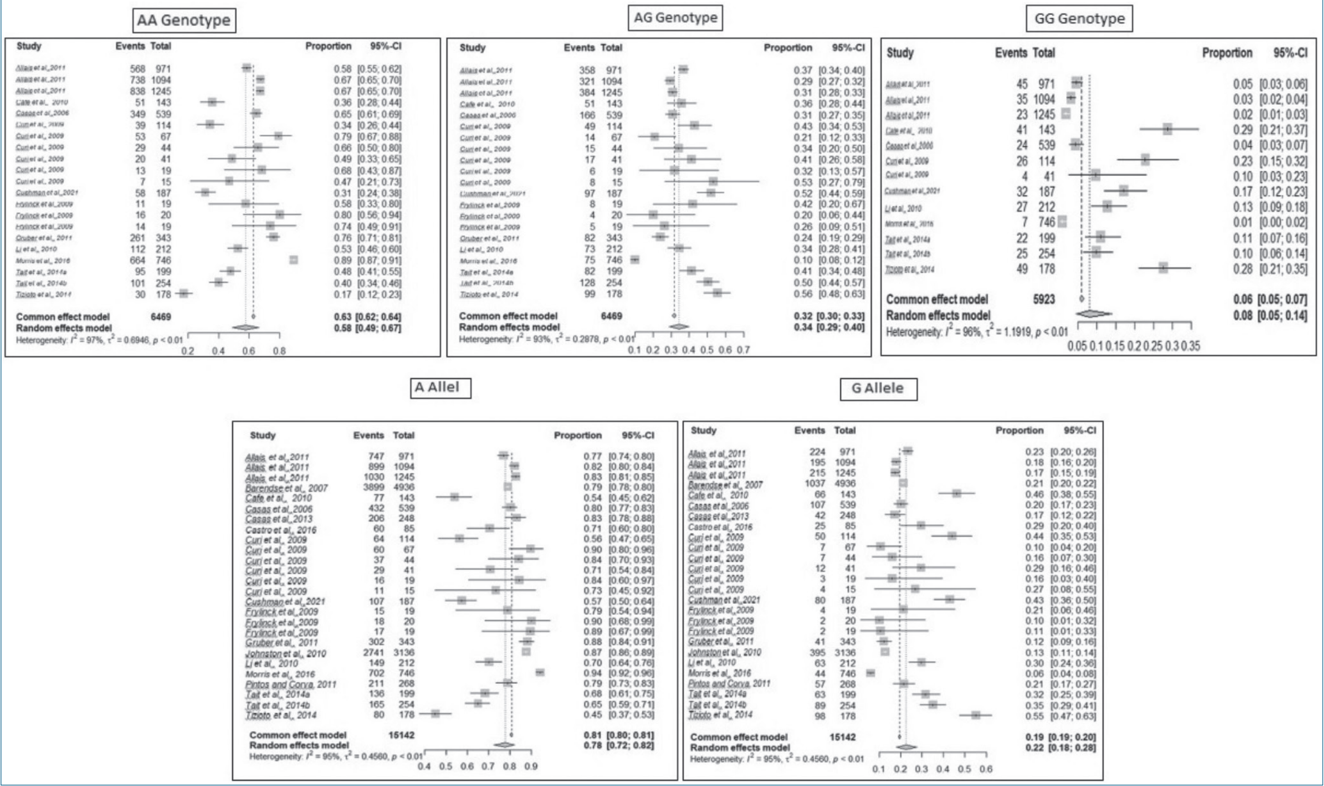

Fig 2. Forest plots of AA, AG, and GG genotypes and A and G alleles of the *CAST* gene

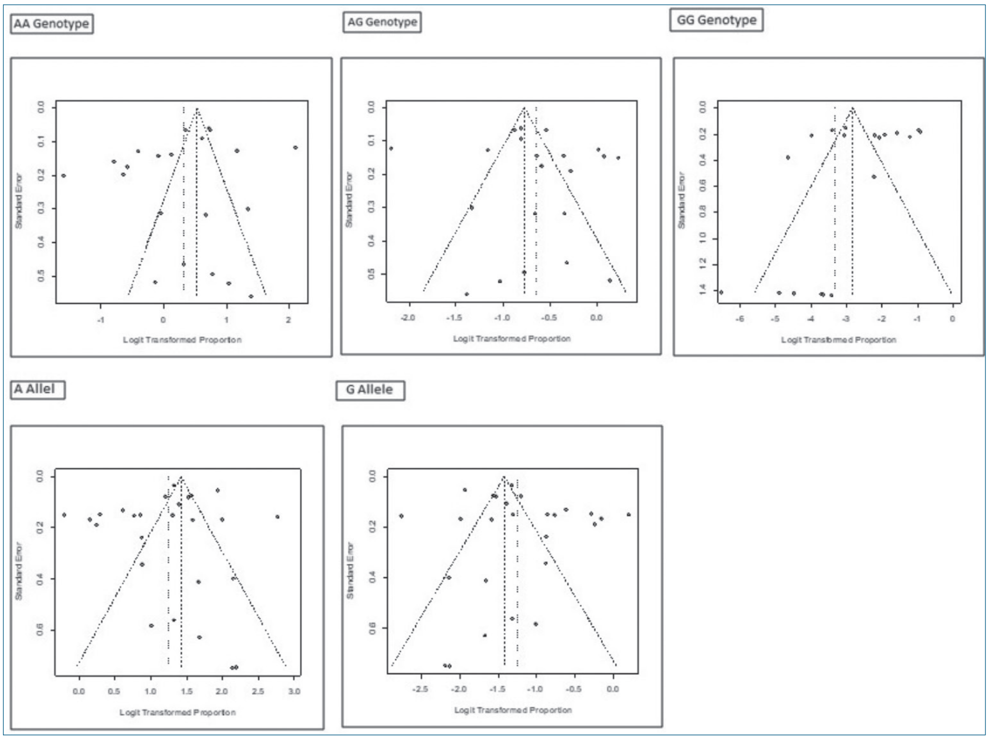

Fig 3. Funnel plots of AA, AG, and GG genotypes and A and G alleles of the *CAST* gene

Table 4. *Meta-analysis results of WBSF values by genotypes of the CAST gene*

Genotype	Number of Study	WBSF	95% CI	Heterogeneity		
				Cochran Q	P Value	I^2 (%)
AA	3	3.707	3.210-4.203	6.99	0.030	71.40
AG	3	3.893	3.762-4.024	0.63	0.728	0.00
GG	2	5.137	4.594-5.679	0.04	0.850	0.00

A and G alleles. Then, as a subgroup analysis, the results of studies giving WBSF values showing the relationship between c.2832A>G polymorphism of the *CAST* gene and meat tenderness were combined.

According to the results of this study, the pooled ratio of AA was 57.8%; however, the AA genotype proportions of individual studies ranged between 17% to 89%. The pooled ratio of AG genotype was 34.2%; however, the AG genotype proportions of individual studies ranged between 10% to 56%. For the GG genotype, the pooled ratio was 8%; however, the GG genotype proportions of individual studies ranged between 1% to 29%. In addition, the pooled ratio was 78%; however, the A allele proportions of individual studies ranged between 45% to 94%. The pooled ratio was 22%; however, the G allele proportions of individual studies ranged between 6% to 55% *(Fig. 2)*. This result shows that different individual studies vary significantly in genotype and allele gene frequencies. Therefore, the need for a meta-analysis of genotype and allele frequencies of *CAST* gene *c.2832A>G* polymorphism in cattle was justified.

Due to the genetic heterogeneity of the cattle breeds used in the studies included in meta-analysis, studies were classified in three groups in order to create more homogeneous subgroups. When the results obtained with this method were examined, it was determined that there was homogeneity between the studies in the *Bos indicus* and cross breed groups. In addition, in contrast to *Bos taurus*, cross breed and total evaluation, the pooled ratio of AG genotype was higher in the *Bos indicus* group than AA and GG genotypes.

According to meta-analysis results, the combined WBSF value for the AA genotype was higher than that observed in Li et al.[21] and lower than in other studies. WBSF value calculated by meta-analysis was very close to the value found by Curi et al.[10]. The results of the two studies for the GG genotype were combined, and the pooled WBSF value was the same as for Li et al.[21]. There was no WBSF value for the GG genotype in the study of Curi et al.[10].

Considering the studies that examined the relationship between the *c.2832A > G* polymorphism of the *CAST* gene and meat tenderness, it was stated that this marker was significantly associated with WBSF. In the study of Li et al.[21], it was noted that the WBSF value did not differ between AA and AG genotypes, and the highest value belonged to the GG genotype, while Curi et al.[10] found that the WBSF value was significantly different between the AA and AG genotypes. The differences in the results show the necessity of the meta-analysis method.

The applications of the meta-analysis method in genetic studies in veterinary medicine are increasing rapidly. While bringing together results of studies on the same subject in genetics, it is necessary to identify studies that examine the same polymorphism of the same gene, and this is quite difficult. There are meta-analysis studies examining the effects of different gene polymorphisms on growth and yield characteristics for different animal species [26,27]. In meta-analysis studies on cattle, growth hormone gene *allul* polymorphism [11], *CSN3* gene polymorphism [12], *Beta-lactoglobulin* gene polymorphism [28], *UASMS2* polymorphism in the *leptin* gene [29], MspI derived variants of growth hormone gene [30] were examined. Especially in studies conducted on cattle, the effects of related genes on milk yield were investigated. Only one of them examined meat quality in cattle [29].

Unlike the others, the *CAST* gene in cattle was considered in this study. Among the many polymorphisms of the *CAST* gene, which were determined to affect meat tenderness, studies in which the *c.2832A>G* polymorphism in cattle were studied were included. Many criteria are examined in studies evaluating meat quality. However, only studies examining the meat tenderness feature were discussed in this study. Also, the association between the *CAST* gene's c.2832A>G polymorphism and meat tenderness has been investigated. Different results were obtained due to sample sizes [7,9,10]. Meta-analysis synthesized the results of the studies examining the relationship between *CAST* gene c.2832A>G polymorphism and meat tenderness in cattle in this research.

This study has some limitations. Because only the articles published in English and Turkish were selected, the results of the studies written in other languages could not be included. In addition, shear force values for very few studies could be obtained due to insufficient information in the analyses for meat tenderness.

In conclusion, with this meta-analysis, the genotype and allele frequencies of a polymorphism of the *CAST* gene and its association with meat tenderness were examined in detail. With the pooled ratio of genotype and allele frequencies and combined mean WBSF values for the AA, AG, and GG genotypes, closer results to the population parameter could be obtained. This study may provide valuable information on improving meat quality in cattle production. This SNP can be used as a reliable genetic marker for meat tenderness as a meat quality trait in cattle breeding.

Availability of Data and Materials

The dataset generated during the current study is available from the corresponding author (E. Uzabaci) on reasonable request.

Ethical Statement

The data for this research were collected from online databases, so this study does not require any ethical permission.

Funding Support

This research received no specific grant from the public, commercial, or not-for-profit funding agencies.

Conflict of Interests

The authors declared that there is no conflict of interest.

Author Contributions

EU, DD: Conception and design; DD: Acquisition of data; EU: Analysis and interpretation of data, writing the article; EU, DD: Final approval of the article.

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