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Relationships between milk protein polymorphisms and production traits in cattle: a systematic review and meta-analysis

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Abstract. Many researchers who have studied the relationships between milk protein polymorphisms and some yield traits in dairy cattle have reported incompatible results. In this study, in order to examine the overall relationships between milk protein genes known as major genes (*CSN1S1, CSN2, CSN3*, and *BLG*) and some yield traits (daily milk yield, lactation milk yield, fat yield, fat content, protein yield, and protein content), a meta-analysis was performed using some genetic models reported in the results of previous studies on cattle. The results suggest that the relationships of major milk protein genes with other factors should be studied using the codominant genetic model in general. Relationships among some *CSN3* genotypes and fat yield, fat content, and protein content, and relationships between some *BLG* genotypes and daily milk yield, fat content, protein yield, and protein content were significant ($P < 0.05$). No significant ($P > 0.05$) relationships were found between these genotypes and other milk production traits. In addition, no significant ($P > 0.05$) relationships between the *CSN1S1* and *CSN2* genotypes with the milk production traits examined were observed.

1 Introduction

For more than 50 years, many studies have reported alternative forms of milk protein genes and examined the relationships between these genetic variants and economic yield traits. Many studies look at the relationship between milk protein genetic variants and various milk production traits. Some authors reported the possibility of using milk protein as a polymorphic genetic marker (Eenennaam and Medrano, 1991; Chung et al., 1996; Kaygisiz and Dogan, 1999; Ikonen et al., 1999; Cardak, 2005; Alipanah et al., 2008; Heck et al., 2009; Mohammadi et al., 2013; Djedovic et al., 2015; Dyman et al., 2015). However, these relationships were reported to be non-significant by other researchers (Sekerden et al., 1999; Jusczak et al., 2001; Micinski et al., 2006; Ozdemir and Dogru, 2007; Gurcan, 2011; Dogru, 2015a; Molee et al., 2015).

Although numerous relationship studies between milk protein gene polymorphic systems and some economic yield traits have been published, the results are conflicting. These discrepancies may be due to differences in the sample size, breeds studied, environmental effects, gene–environment interactions, and study designs. The conflicting results of these studies, which are performed and frequently repeated in various countries, do not benefit breeders.

Meta-analysis is a test method in which the results of many studies performed in the field are used, which offers more powerful results. Importantly, the different studies used can utilize different samples and the results can be conflicting. Meta-analysis is beneficial for studies intensively repeated with an insufficient number of samples and for those in which the results are not in the proper format because sufficient criteria have been generated for the meta-analysis when the results of many studies are used. Different individual study results are combined and analyzed in the meta-analysis. Then, it is possible to achieve more powerful results in experiments using this analysis due to the randomness and sufficient sample size.

Meta-analysis has a number of potential advantages. These are an increase in power, an enhancement in accuracy, the ability to answer questions that are not responded to by individual studies, and the opportunity to resolve controversies that originate from contradictory requirements. Nevertheless, meta-analysis also has some disadvantages, one of which is the risk of serious misleading, especially when specific study designs, such as within-study biases, variation across studies, and reporting biases are not carefully analyzed. Being familiar with the type of data (e.g., categorical or continuous) which result from the measurement of an outcome in an individual study and choosing the appropriate effect measures in order to compare intervention groups bear great importance. The majority of meta-analysis methods represent variations on a weighted average of the effect estimates from various studies.

In this study, the aim was to conduct a meta-analysis on the results of previous dairy cattle studies with the purpose of analyzing the overall relationships between milk protein genes, which are known as major genes (*alphas1-casein* (*αs1-CN*, *CSN1S1*), *beta-casein* (*β-CN, CSN2*) *kappa-casein* (*κ-CN*, *CSN3*) and *beta-lactoglobulin* (*β-LG*, *BLG*)), and a number of production traits.

2 Materials and methods

2.1 Materials and data extraction

Scientific journals were searched for published papers in English on genetic relationships between milk protein polymorphism and milk production traits in several databases (Web of Science, Science Direct, and Google Scholar), and 120 original publications from 1986 to 2016 were collected; the number of articles has been reduced for reasons such as suitability to criteria used and the presentation of results, and 40 papers were chosen. Of the collected publications, 15 consisted of *alphas1-casein* (10 506 yield records), 13 of them consisted of *beta-casein* (nearly 2223 yield records), 32 of them consisted of *kappa-casein* (nearly 7883 yield records), and 28 of them consisted of *beta-lactoglobulin* (nearly 2598 yield records). All selected papers met the three following criteria: (1) the relationship between milk protein polymorphism and milk production traits (daily milk, lactation milk yield, fat yield, fat content, protein yield, and protein content), (2) number of genotypes per animal breeds, and (3) the average and standard deviation or error of the related yield trait of each genotype (standard errors were converted to standard deviations using a statistical formula).

We extracted study content and data independently using a standard form prepared in Excel. The content of the studies included the first author's name, year of publication, country, breed, number of animals examined, number of genotypes, Hardy–Weinberg equilibrium, mean of the related yield traits of genotypes, standard deviation of means, and statistical significance level of the relationship. For the statistical analysis, this information was carefully organized by authors in order to avoid errors.

2.2 Statistical analysis

All statistical analyses were conducted using STATA version 11.2 (StataCorp 2001; Stata Statistical Software). A p value less than 0.05 was accepted as statistically significant.

The data set was separately organized for each gene region, and the methods below were followed.

- In the meta-analysis, the analysis of differences between means is performed using a random or fixed model. Model selection was based on whether the effects of the studies were homogeneous or heterogeneous (Higgins and Thompson, 2002). The fixed model was used when the study results were homogeneous, and the random model was used when they were heterogeneous. The heterogeneity assumption was calculated based on I^2 statistics (for the test of heterogeneity, the significant level (P) was set as 0.10).
- The heritage pattern of the alleles to be used in this study was examined as dominant (AA + AB versus BB), completely overdominant (AA + BB versus AB), recessive (AA versus AB + BB), or codominant (AA versus AB, AA versus BB, and AB versus BB).
- In the analysis of factors, genotype differences related to yield trait were evaluated separately according to the growing types of cattle breeds (dairy subgroup: dairy cattle breeds; other subgroup: dual purpose breeds, various crossbreeds; overall).
- The standard mean differences (SMDs) and standard errors were calculated with a 95 % CI (confidence interval) to evaluate the strength of the relationship among the yield trait means of each of the gene variants examined. This procedure was used in the comparison of multiple pairwise variants.
- In the calculation of SMD, the Cohen method (Cohen, 1988) was used when the number of studies was greater than 10, and the Hedges method (Hedges, 1981) was used when it was lower than 10. In cases in which the number of studies was > 10, the Cohen method for standardized mean differences was advantageous because it has a tendency to overestimate the effect of size. However, if the number of studies is small, the Hedges method for standardized mean differences is advantageous (DeCoster 2009; Borenstein et al., 2009).

3 Results and discussion

The data sets used in this study were organized separately by economic production traits, loci, and genetic models. The dominant (AA + AB versus BB), completely overdominant (AA + BB versus AB), recessive (AA versus AB + BB), and codominant (AA versus AB, AA versus BB, and AB versus BB) statuses of the alleles were taken into consideration before the statistical evaluation (Table 1). According to the analysis results, evaluations were mainly carried out based on this model in the paper because the relevant alleles generally exhibited the codominant trait.

The number of studies and the meta-analysis results in which different methods (Cohen or Hedges) were used based on whether the studies were homogeneous or heterogeneous are presented in Tables 1, 2, 3, 4, and 5. The heterogeneity test, SMD, 95 % CI values, its % weight, and P values of the pairwise comparisons are presented in the tables as well.

3.1 Analysis of *CSN3* genotypes

Using 13 studies, no significant relationships could be determined between *CSN3* genotypes (AA vs. AB, AA vs. BB, and AB vs. BB) and daily milk yield in all cattle and subgroups ($P > 0.05$). In terms of daily milk yield, although the ranking was observed to be AA > AB > BB in the dairy group, it was observed to be exactly the opposite in the other group. However, when analyses were performed according to the recessive model, the dairy subgroup AA vs. AB + BB genotype mean difference was found to be statistically significant ($P < 0.05$) and was observed to provide advantages in favor of AA (Table 1). In some individual studies performed previously, it was reported that *CSN3* AA and AB genotypes had superiority (Cardak, 2005; Pawelska-Goral et al., 2008; Bartonova et al., 2012; Molee et al., 2015). Some researchers reported that daily milk yield means were not significant among *CSN3* genotypes (Dogru, 1994; Ozdemir and Dogru, 2005; Gurcan, 2011).

When 28 studies were used, a significant relationship could not be determined between *CSN3* genotypes and lactation milk yield in all cattle and milk type cattle groups ($P > 0.05$). In the analysis performed according to the recessive genetic model, a significant difference was observed in favor of the AA-only genotype in the other subgroup ($P < 0.05$); significant differences among groups were not observed when compared to other models ($P > 0.05$). In the individual studies performed, some authors reported that lactation milk yield means were significant among *CSN3* genotypes (Dogan and Kaygisiz, 1999; Alipanah et al., 2008; Djedovic et al., 2015), and other authors reported that mean differences were not significant (Eenennaam and Medrano, 1991; Bovenhuis et al., 1992; Kaygisiz et al., 1999; Ozdemir and Dogru, 2005; Dogru, 2015a).

Using 20 studies, a significant relationship could not be established between *CSN3* genotypes and fat yield in all cattle ($P > 0.05$); however, the AA vs. AB genotype fat yield means were found statistically different ($P < 0.05$) and the AA genotype was found superior in the dairy subgroup. In the other subgroup, statistically significant relationships were not determined between fat yield means belonging to genotypes ($P > 0.05$). According to the completely overdominant model, statistical significance was determined against AB in the dairy subgroup and in favor of the AB variant in the other subgroup ($P < 0.05$). In the analysis performed according to the recessive model, while a significance in favor of the AA genotype was determined in dairy subgroup, a significant difference for only the AA genotype was found in the other subgroup ($P < 0.05$). In the individual studies performed, while some authors reported that fat yield means were significant among the *CSN3* genotypes and reported a superiority in favor of the AB genotype (Alipanah et al., 2008; Dogru, 2015a; Djedovic et al., 2015), other authors reported that the mean differences were not significant (Eenennaam et al., 1990; Bovenhuis et al., 1992; Cardak, 2005; Ozdemir and Dogru, 2005; Zhang et al., 2007; Heck et al., 2009; Alim et al., 2015). Consequently, as a result of the meta-analysis performed, the use of the *CSN3* AB variant in programs that seek to improve fat yield will be useful as an indirect marker.

A total of 32 studies were used to assess the relationship between *CSN3* genotypes and fat content. A statistically significant relationship ($P < 0.05$) was determined between AA vs. BB genotypes in all cattle and fat content and between AA vs. BB and AB vs. BB genotypes in the dairy subgroup. Significant differences could not be found in terms of fat content in the other groups examined or among the other genotypes. Among all the models analyzed, only the dominant model revealed that the BB genotype in all the cattle and the dairy subgroup was different.

According to our results, there is a selection advantage in favor of BB genotype for milk fat content, and it can be used as a marker gene. In the individual studies performed, some authors reported that the fat content means were significantly different among the *CSN3* genotypes and reported a superiority in favor of the BB genotype (Bovenhuis et al., 1992; Alipanah et al., 2008; Dogru, 2015a); other authors reported that the mean differences were not significant (Eenennaam and Medrano, 1991; Cardak, 2005; Ozdemir and Dogru, 2005; Zhang et al., 2007; Heck et al., 2009; Djedovic et al., 2015).

The mean differences of the genotype groups examined for protein yield were found not significant according to all the genetic models ($P > 0.05$). In individual studies performed, some authors reported differences between protein yield means and different *CSN3* genotypes, including a significant preference for the BB genotype (Eenennaam and Medrano, 1991; Alim et al., 2015); however, other authors did not find these differences significant (Bovenhuis et al., 1992; Micinski et al., 2006; Alipanah et al., 2008).

In the analysis in which 24 studies were used for assessing the relationship between *CSN3* genotypes and protein content, a statistically high significant relationship ($P < 0.01$) was determined between AA vs. BB and AB vs. BB genotypes in all cattle in terms of protein content. The relationship between AA vs. AB was found not significant ($P > 0.05$) and the genotypic ranking in terms of protein content was found to be BB > AB > AA. A statistically significant relationship was determined between the protein content values and all *CSN3* genotypes in the dairy subgroup, and the rank-

Table 1. Genetic model analyses of the genotypes related to *BLG, CSN2*, and *CSN3*.

Genotype	Traits	Type		AA + AB versus BB, dominant model						AA versus AB + BB, recessive model						AA + BB versus AB, completely overdomn. model					
			n	I^2	SMD	95 %	CI	% Weight	*p*	I^2	SMD	95 %	CI	% Weight	*p*	I^2	SMD	95 %	CI	% Weight	*p*
CSN3	Daily milk yield	Dairy	8	0.0	0.071	−0.062	0.204	74.47	0.295	28.0	0.09	0.010	0.173	86.24	0.027	47.6*	0.067	−0.015	0.149	83.62	0.111
		Other	3	63.5*	−0.11	−0.332	0.122	25.53	0.365	0.0	−0.1	−0.317	0.091	13.76	0.278		−0.023	−0.209	0.162	16.38	0.805
		Overall	11	0.0	0.026	−0.089	0.141	100.00	0.655	29.4	0.06	−0.012	0.139	100.00	0.100	28.8	0.052	−0.023	0.127	100.00	0.175
	Lactation milk yield	Dairy	18	34.7*	0.079	−0.039	0.196	69.00	0.191	47.0*	0.06	−0.018	0.138	71.36	0.130	42.5*	0.029	−0.047	0.106	69.86	0.449
		Other	10	60.8*	−0.11	−0.35	0.132	31.00	0.374	33.2	−0.2	−0.288	−0.014	28.64	0.031	0.6	−0.066	−0.157	0.024	30.14	0.150
		Overall	28	47.6**	0.022	−0.087	0.132	100.00	0.691	51.8**	0	−0.069	0.076	100.00	0.918	36.6*	0.002	−0.06	0.064	100.00	0.952
	Fat yield	Dairy	13	70.5**	0.033	−0.167	0.233	64.36	0.746	75.4**	0.13	0.006	0.255	72.05	0.040	76.4**	0.132	0.003	0.261	68.82	0.046
		Other	7	8.9	0.002	−0.13	0.133	35.64	0.980	0.0	−0.3	−0.409	−0.133	27.95	0.000	0.0	−0.18	−0.291	−0.069	31.18	0.001
		Overall	20	61.1**	0.018	−0.118	0.154	100.00	0.800	74.3**	0.02	−0.091	0.135	100.00	0.703	73.5**	0.035	−0.073	0.143	100.00	0.524
	Fat content	Dairy	22	54.5**	−0.161	−0.294	−0.03	66.94	0.018	56.3**	−0	−0.100	61	75.07	0.636	25.0	−0.002	−0.039	0.035	85.28	0.909
		Other	10	0.0	−0.01	−0.115	0.1	33.06	0.887	0.0	−0	−0.110	0.100	24.93	0.923		0.003	−0.087	0.093	14.72	0.947
		Overall	32	45.6**	−0.1	−0.2	−0.01	100.00	0.035	42.6**	−0	−0.078	0.049	100.00	0.654	12.1	−0.001	−0.036	0.033	100.00	0.936
	Protein yield	Dairy	8	48.5*	−0.07	−0.266	0.125	81.80	0.478	16.0	0	−0.041	0.043	96.85	0.966	50.0*	0.06	−0.044	0.163	87.71	0.258
		Other	1		0.03	−0.23	0.29	18.2	0.819		−0.1	−0.322	0.147	3.15	0.464		−0.085	−0.29	0.119	12.29	0.413
		Overall	9	41.6*	−0.04	−0.201	0.114	100.00	0.588	9.7	−0	−0.044	0.04	100.00	0.930	45.7*	0.037	−0.054	0.129	100.00	0.425
	Protein content	Dairy	17	75.2**	−0.33	−0.520	−0.13	80.23	0.001	53.4**	−0.1	−0.221	−0.064	79.83	0.000	46.6*	−0.048	−0.122	0.026	79.14	0.207
		Other	3	37.5	−0.14	−0.378	0.095	19.77	0.241	86.5**	0.07	−0.292	0.44	20.17	0.692	73.9**	0.133	−0.116	0.381	20.86	0.295
		Overall	20	72.2**	−0.28	−0.438	−0.11	100.00	0.001	68.1**	−0.1	−0.192	−0.021	100.00	0.015	58.5**	−0.009	−0.085	0.068	100.00	0.827
BLG	Daily milk yield	Dairy	6	68.8**	0.137	−0.112	0.386	59.55	0.281	70.7**	−0.1	−0.418	0.208	58.19	0.512	17.8	−0.186	−0.33	−0.043	59.83	0.011
		Other	4	0.0	0.027	−0.138	0.192	40.45	0.747	48.7	−0.4	−0.642	−0.078	41.81	0.012	65.3*	−0.28	−0.554	−0.005	40.17	0.046
		Overall	10	50.3*	0.099	−0.052	0.25	100.00	0.200	69.2**	−0.2	−0.439	0.025	100.00	0.080	41.3*	−0.221	−0.354	−0.088	100.00	0.001
	Lactation milk yield	Dairy	17	73.9**	0.092	−0.023	0.207	64.36	0.118	70.1**	0.14	−0.013	0.284	62.39	0.075	0.0	−0.019	−0.045	0.008	63.48	0.177
		Other	9	96.7**	−0.37	−0.869	0.121	36.66	0.138	96.4**	0.09	−0.426	0.601	37.61	0.738	97.9**	0.3	−0.274	0.874	36.52	0.306
		Overall	26	92.3**	−0.05	−0.2	0.106	100.00	0.546	90.9**	0.13	−0.058	0.309	100.00	0.181	93.7**	0.1	−0.06	0.26	100.00	0.222
	Fat yield	Dairy	11	84.8**	0.012	−0.225	0.248	57.89	0.923	93.7**	0.3	−0.171	0.777	59.03	0.211	87.0**	0.247	−0.006	0.5	56.52	0.056
		Other	6	14.3	0.035	−0.059	0.129	42.11	0.470	61.8*	−0	−0.204	0.152	40.97	0.776	62.8*	−0.055	−0.198	0.088	43.48	0.451
		Overall	17	78.3**	0.023	−0.101	0.148	100.00	0.714	90.7**	0.18	−0.050	0.412	100.00	0.125	83.1**	0.107	−0.026	0.239	100.00	0.114
	Fat content	Dairy	19	84.5**	−0.167	−0.309	−0.03	69.18	0.021	28.8	−0.1	−0.222	−0.047	69.58	0.003	85.6**	0.064	−0.08	0.207	68.34	0.386
		Other	8	89.7**	−0.18	−0.494	0.144	30.82	0.282	77.0**	0.05	−0.219	0.317	30.42	0.718	74.8**	0.147	−0.05	0.344	31.66	0.144
		Overall	27	85.8**	−0.17	−0.288	−0.04	100.00	0.008	56.9**	−0.1	−0.186	0.006	100.00	0.065	83.1**	0.091	−0.019	0.201	100.00	0.106
	Protein yield	Dairy	6	90.6**	0.131	−0.175	0.438	64.31	0.402	97.1**	0.37	−0.196	0.935	65.77	0.200	87.8**	0.11	−0.12	0.34	64.51	0.349
		Other	3	0.0	−0.02	−0.125	0.086	35.69	0.716	76.8*	−0.2	−0.546	0.116	34.23	0.203	0.0	−0.05	−0.147	0.047	35.49	0.315
		Overall	9	85.9**	0.039	−0.134	0.212	100.00	0.660	95.7**	0.15	−0.199	0.495	100.00	0.404	81.3**	0.013	−0.122	0.149	100.00	0.846
	Protein content	Dairy	15	97.4**	0.003	−0.181	0.187	77.62	0.975	94.1**	0.21	0.003	0.415	77.11	0.047	96.4**	0.118	−0.042	0.279	77.11	0.149
		Other	4	79.5**	−0.29	−0.569	−0.01	22.38	0.046	0.0	−0	−0.165	0.079	22.89	0.489	61.0*	0.158	−0.025	0.342	22.89	0.091
		Overall	19	96.7**	−0.06	−0.221	0.093	100.00	0.424	92.5**	0.14	−0.027	0.31	100.00	0.100	95.5**	0.135	−0.001	0.271	100.00	0.052
CSN2	Daily milk yield	Dairy	2	0.0	0.029	−0.97	1.028	45.15	0.955	0.0	−0.1	−0.259	0.158	53.02	0.634	0.0	−0.054	−0.266	0.158	52.52	0.619
		Other	2		0.158	−0.748	1.064	54.85	0.733	84.0**	0.25	−0.215	0.721	46.98	0.289	85.1**	0.25	−0.235	0.735	47.48	0.312
		Overall	4	0.0	0.099	−0.572	0.77	100.00	0.771	65.1**	0.1	−0.142	0.348	100.00	0.410	67.0**	0.101	−0.154	0.357	100.00	0.437
	Lactation milk yield	Dairy	7	0.0	−0.02	−0.953	0.908	52.51	0.816	0.0	0.01	−0.144	0.158	38.18	0.927	54.3*	−0.228	−0.646	0.189	24.78	0.283
		Other	6	91.8**	0.022	−0.16	0.203	47.49	0.963	85.9**	0.08	−0.218	0.376	61.82	0.603	2.3	0.195	0.091	0.298	75.22	0.000
		Overall	13	79.8**	−0.02	−0.444	0.409	100.00	0.936	74.5**	0.04	−0.147	0.234	100.00	0.653	48.9*	0.101	−0.052	0.254	100.00	0.195
	Fat yield	Dairy	5	27.0	0.086	−0.283	0.455	80.90	0.649	89.3**	−0.6	−1.296	0.049	67.12	0.069	89.7**	−0.606	−1.327	0.114	66.84	0.099
		Other	2	0.0	0.009	−0.75	0.769	19.10	0.981	0.0	0.3	0.040	0.552	32.88	0.023	0.0	0.298	0.04	0.555	33.16	0.023
		Overall	7	0.0	0.071	−0.261	0.403	100.00	0.675	86.5**	−0.3	−0.726	0.151	100.00	0.199	87.2**	−0.282	−0.747	0.183	100.00	0.235
	Fat content	Dairy	8	0.0	−0.05	−0.404	0.309	86.58	0.794	0.0	−0	−0.138	0.122	60.65	0.902	0.0	−0.003	−0.14	0.134	59.80	0.966
		Other	4		−0.05	−0.853	0.859	13.42	0.919	83.5**	0.07	−0.391	0.528	39.35	0.770	83.4**	0.069	−0.389	0.527	40.20	0.768
		Overall	12	0.0	−0.047	−0.379	0.284	100.00	0.779	49.8*	0.04	−0.133	0.204	100.00	0.679	50.6*	0.042	−0.132	0.216	100.00	0.635
	Protein content	Dairy	6	0.0	−0	−0.382	0.381	100.00	0.997	0.0	−0	−0.162	0.106	72.46	0.683	0.0	−0.031	−0.172	0.11	72.23	0.667
		Other	2		0			0.00		87.0**	0.37	−0.358	1.107	27.54	0.317	86.4**	0.367	−0.351	1.084	27.77	0.317
		Overall	8	0.0	−0	−0.382	0.381	100.00	0.997	60.6*	0.09	−0.134	0.303	100.00	0.448	59.2*	0.083	−0.136	0.301	100.00	0.457

* $p<0.10$. ** $P<0.01$. *n* number of publication.

ing of genotypes was observed to be BB > AB > AA (Table 1). A significant relationship could not be determined between the protein content means and any of the genotypes in the other subgroup ($P>0.05$). The BB variant was seen as advantageous when the analysis was performed according to the dominant model, and a significant relationship against the AA variant was found when the recessive model was used (Table 1). Based on the results for other genetic models, the use of the *CSN3* B allele as a marker to improve milk protein content in dairy cattle breeds should be considered.

3.2 Analysis of *BLG* genotypes

A total of 10 studies were used to assess the relationship between *BLG* genotype (AA vs. AB, AA vs. BB, and AB vs. BB) and daily milk yield, and highly significant differences were observed in all cattle and subgroups ($P<0.01$). Although only the difference among the AB vs. BB genotypes was found significant in the dairy subgroup ($P<0.01$), the differences between the means of AA vs. AB ($P<0.01$) and AA vs. BB ($P<0.05$) genotypes were found to be significant in the other subgroup. Although the differences between AA vs. AB ($P<0.05$) and AB vs. BB ($P<0.01$) genotype means were significant in all cattle, a difference among AA vs. BB means was not significant ($P>0.05$). In terms of daily milk yield, AB > BB > AA. When using the completely overdominant model, the mean was found to be statistically superior in favor of AB. In individual studies performed, some researchers reported that the daily milk yield means were significant among *BLG* genotypes (Cardak, 2005; Molee et al., 2015); however, other researchers

Table 2. Results of the meta-analysis on associations among *CSN3* genotypes and milk production traits, SMD values, and level of significance.

Traits	Type		AA versus AB						AA versus BB						AB versus BB					
		n	I^2	SMD	95 %	CI	% Weight	p	I^2	SMD	95 %	CI	% Weight	p	I^2	SMD	95 %	CI	% Weight	p
Daily milk yield	Dairy	9	38.0	0.086	−0.001	0.17	86.48	0.052	0.0	0.057	−0.085	0.200	81.21	0.432	0	0.07	−0.08	0.212	74.59	0.378
	Other	4	0	−0.1	−0.314	0.12	13.52	0.390	61.0*	−0.15	−0.447	0.146	18.79	0.320	64.5*	−0.01	−0.26	0.243	25.41	0.956
	Overall	13	24.4	0.061	−0.019	0.14	100.00	0.135	0.0	0.018	−0.110	0.147	100.00	0.782	0	0.05	−0.08	0.174	100.00	0.464
Lactation milk yield	Dairy	18	38.9*	0.048	−0.029	0.13	72.65	0.218	31.3	0.06	−0.060	0.186	71.54	0.316	14.1	0.08	0.00	0.165	70.93	0.056
	Other	10	14.4	−0.07	−0.189	0.05	27.35	0.260	60.2*	−0.08	−0.375	0.211	28.46	0.583	53.0*	0.03	−0.10	0.164	29.07	0.614
	Overall	28	35.5**	0.015	−0.051	0.08	100.00	0.649	43.1**	0.03	−0.092	0.144	100.00	0.663	27.6	0.07	0.00	0.138	100.00	0.06
Fat yield	Dairy	13	74.9**	0.146	0.014	0.28	72.20	0.030	67.7**	0.04	−0.162	0.251	67.85	0.674	74.9**	−0.03	−0.27	0.211	64.14	0.819
	Other	7	46.0*	−0.21	−0.443	0.01	27.80	0.066	11.3	−0.09	−0.273	0.098	32.15	0.356	0.8	0.11	−0.02	0.235	35.86	0.107
	Overall	20	71.5**	0.050	−0.066	0.17	100.00	0.399	59.8**	0.00	−0.158	0.153	100.00	0.975	66.9**	0.03	−0.13	0.19	100.00	0.726
Fat content	Dairy	22	37.4*	−0.010	−0.048	0.03	89.21	0.612	64.2**	−0.20	−0.358	−0.03	70.32	0.018	36.9*	−0.13	−0.25	−0.01	65.95	0.034
	Other	10	0	−0.02	−0.127	0.09	10.79	0.765	0.0	−0.10	−0.246	0.043	29.68	0.169	27	−0.01	−0.15	0.138	34.05	0.915
	Overall	32	25.0	−0.01	−0.047	0.03	100.00	0.564	54.9**	−0.16	−0.280	−0.04	100.00	0.011	34.4*	−0.09	−0.18	0.008	100.00	0.073
Protein yield	Dairy	8	44.0*	0.004	−0.040	0.05	96.81	0.855	41.2	−0.02	−0.115	0.077	91.25	0.703	50.5*	−0.1	−0.32	0.114	81.34	0.358
	Other	1		0.066	−0.179	0.310	3.19	0.599		−0.13	−0.178	0.443	8.75	0.404		0.06	−0.21	0.335	18.66	0.641
	Overall	9	37.1	0.006	−0.038	0.05	100.00	0.785	37.2	−0.01	−0.097	0.086	100.00	0.907	44.7*	−0.06	−0.23	0.116	100.00	0.516
Protein content	Dairy	19	42.8*	−0.10	−0.170	−0.02	79.19	0.012	84.0***	−0.43	−0.674	−0.18	82.74	0.001	71.2**	−0.26	−0.46	−0.07	79.45	0.008
	Other	5	97.4***	−0.23	−1.094	0.64	20.81	0.608	97.3*	0.75	−2.205	0.712	17.26	0.316	0	−0.14	−0.33	0.04	20.55	0.125
	Overall	24	88.2***	−0.12	0.256	0.02	100.00	0.095	89.9***	−0.50	−0.775	−0.22	100.00	0.001	66.5**	−0.23	−0.39	−0.07	100.00	0.006

* $p<0.10$. ** $P<0.01$. n number of publication.

reported that the mean differences were not significant (Sekerden et al., 1999; Ozdemir and Dogru, 2007).

In the analysis in which 26 studies were used, a significant relationship was not observed between *BLG* genotypes and lactation milk yield in all cattle ($P>0.05$); however, a statistically significant relationship ($P<0.05$) was observed between AA vs. AB genotypes in the milk type group and between AA vs. BB genotypes in the other subgroup in terms of milk yield means. Superiority was observed in favor of AA for the dairy subgroup and in favor of BB for the other subgroup. The differences among lactation milk yield means for the other genotype pairs examined were not significant ($P>0.05$). Similar results were observed in the analyses performed according to the other genetic models. In the individual studies performed, some researchers reported that the differences in lactation milk yield means among *BLG* genotypes were significant (Kaygisiz et al., 1999; Ojala et al., 2004; Heidari et al., 2009), yet other researchers reported that mean differences were not significant (Eenennaam and Medrano, 1991; Ozdemir and Dogru, 2007; Dokso et al., 2011; Dogru, 2015b).

In the analysis in which 17 studies were used, a significant relationship was not observed between *BLG* genotypes and fat yield in the subgroups ($P>0.05$). Although a statistically significant relationship ($P<0.05$) was determined among AA vs. AB genotype means in all cattle, significant differences were not found among the other genotype means. The differences among the genotype means compared were not found significant in the analyses performed according to other genetic models. In the individual studies performed, some researchers reported the differences between fat yield means and *BLG* genotypes as significant and in favor of the BB genotype (Ojala et al., 2004; Felenczak et al., 2008), yet other researchers could not find significant differences (Eenennaam and Medrano, 1991; Ozdemir and Dogru, 2007; Micinski et al., 2006; Czerniawska et al., 2011; Dogru, 2015b).

A total of 27 studies were used to assess the relationship between the *BLG* genotypes and fat content. Although a statistically significant relationship ($P<0.01$) was found between AA vs. BB ($P<0.01$) and AB vs. BB ($P<0.05$) genotypes in all cattle in terms of fat content and among AA vs. BB genotypes in the dairy subgroup, significant differences were not found in terms of fat content between the genotypes in the other subgroup ($P>0.05$). When the analysis was performed according to the dominant model, the fat content values of the BB variant were higher, and the difference was statistically significant. Using the recessive model, the AB + BB variant in the dairy subgroup was also statistically superior when compared to the fat content value of the AA variant (Table 1). These results suggest that the *BLG* B allele can be used as a genetic marker in programs that seek to alter fat content. In the individual studies performed, some researchers reported that the *BLG* BB variant was significantly advantageous in terms of fat content values (Juszczak et al., 2001; Ojala et al., 2004; Czerniawska et al., 2011; Molee et al., 2015). However, other studies reported that the differences among the fat content values of the different genotypes were not significant (Eenennaam and Medrano, 1991; Felenczak et al., 2008; Micinski et al., 2006; Ozdemir and Dogru, 2007; Dokso et al., 2011; Dogru, 2015b).

In the groups examined, while *BLG* was seen as AA > AB > BB among the protein yield means of all genotypes, differences among mean values were not statistically significant ($P>0.05$). The differences among the protein yield means of *BLG* genotypes compared were not found significant in the analyses performed according to other genetic models ($P>0.05$). In individual studies performed, while the differences among protein yield means of *BLG* genotypes were reported to be significant in some studies (Ojala et al.,

Table 3. Results of the meta-analysis on the associations among *BLG* genotypes and milk production traits, SMD values, and level of significance.

Traits	Type		AA versus AB						AA versus BB						AB versus BB					
		n	I^2	SMD	95 %	CI	% Weight	p	I^2	SMD	95 %	CI	% Weight	p	I^2	SMD	95 %	CI	% Weight	p
Daily milk yield	Dairy	6	55.9*	−0.16	−0.435	0.122	58.54	0.270	79.4**	−0.01	−0.441	0.420	58.20	0.962	36.8	0.217	0.071	0.364	59.95	0.004
	Other	4	54.7*	−0.44	−0.764	−0.110	41.66	0.009	0	−0.25	−0.476	−0.030	41.80	0.026	9.8	0.165	−0.015	0.344	40.05	0.072
	Overall	10	62.6**	−0.28	−0.505	−0.045	100.00	0.019	69.3**	−0.1	−0.370	0.164	100.00	0.448	21.3	0.196	0.083	0.309	100.00	0.001
Lactation milk yield	Dairy	17	45.5*	0.127	0.003	0.250	62.24	0.044	71.4**	0.173	0.000	0.347	60.37	0.051	54.9**	0.076	−0.022	0.174	63.90	0.127
	Other	9	97.3**	0.201	−0.446	0.848	37.76	0.543	51.4*	−0.234	−0.405	−0.064	39.63	0.007	96.9**	−0.414	−0.978	0.151	36.10	0.151
	Overall	26	92.2**	0.162	−0.053	0.377	100.00	0.139	73.0**	0.007	−0.125	0.139	100.00	0.914	91.8**	−0.048	−0.210	0.114	100.00	0.563
Fat yield	Dairy	11	90.1**	0.412	−0.027	0.852	55.82	0.066	91.6**	0.322	−0.157	0.800	58.50	0.188	83.8**	−0.113	−0.369	0.144	56.51	0.389
	Other	6	68.4**	−0.07	−0.280	0.139	44.18	0.509	41.9	−0.021	−0.189	0.147	41.50	0.807	37.9	0.065	−0.061	0.191	43.49	0.311
	Overall	17	86.6**	0.218	0.002	0.434	100.00	0.047	87.5**	0.176	−0.056	0.408	100.00	0.136	78.1**	−0.011	−0.146	0.124	100.00	0.871
Fat content	Dairy	19	70.9**	−0.02	−0.174	0.131	68.30	0.778	60.7**	−0.245	−0.381	−0.109	69.30	0.000	88.5**	−0.146	−0.325	0.033	68.28	0.109
	Other	8	66.6**	0.097	−0.144	0.338	31.70	0.429	84.4**	−0.035	−0.402	0.332	30.70	0.851	86.3**	−0.209	−0.508	0.089	31.72	0.169
	Overall	27	69.3**	0.014	−0.109	0.137	100.00	0.825	72.7**	−0.18	−0.313	−0.047	100.00	0.008	87.5**	−0.165	−0.306	−0.024	100.00	0.022
Protein yield	Dairy	6	96.1**	0.326	−0.190	0.842	65.54	0.215	96.7**	0.513	−0.170	1.197	65.21	0.141	68.2**	0.013	−0.171	0.198	63.98	0.887
	Other	3	72.1*	−0.21	−0.530	0.105	34.46	0.190	75.0*	−0.214	−0.585	0.157	34.79	0.259	0	0.008	−0.102	0.119	36.02	0.884
	Overall	9	94.3**	0.113	−0.205	0.431	100.00	0.487	95.1**	0.217	−0.174	0.608	100.00	0.277	51.4*	0.006	−0.096	0.109	100.00	0.904
Protein content	Dairy	15	84.9**	0.198	0.045	0.350	75.61	0.011	99.2**	0.037	−0.537	0.612	78.51	0.899	96.6**	−0.126	−0.302	0.050	77.09	0.162
	Other	4	0	0.008	−0.120	0.136	24.39	0.898	66.5*	−0.255	−0.546	0.036	21.49	0.085	76.3**	−0.281	−0.559	−0.003	22.91	0.047
	Overall	19	80.9**	0.148	0.024	0.273	100.00	0.019	99.1**	−0.039	−0.517	0.439	100.00	0.872	95.7**	−0.164	−0.314	0.013	100.00	0.033

* $p<0.10$. ** $P<0.01$. n number of publication.

Table 4. Results of the meta-analysis on associations among *CSN2* genotypes and milk production traits, SMD values, and level of significance.

Traits	Type		AA versus AB						AA versus BB						AB versus BB					
		n	I^2	SMD	95 %	CI	% Weight	p	I^2	SMD	95 %	CI	% Weight	p	I^2	SMD	95 %	CI	% Weight	p
Daily milk yield	Dairy	6	0	−0.054	−0.266	0.158	52.56	0.618	0	0.024	−0.976	1.025	46.66	0.962	0	0.123	−1.025	1.271	39.8	0.834
	Other	4	84.6**	0.254	−0.227	0.735	47.44	0.300		0.146	−0.79	1.082	53.34	0.759		0.168	−0.765	1.101	60.2	0.725
	Overall	10	66.4**	0.103	−0.151	0.358	100	0.426	0	0.09	−0.594	0.773	100	0.797	0	0.15	−0.574	0.874	100	0.685
Lactation milk yield	Dairy	6	53.0*	−0.21	−0.621	0.202	32.05	0.318	0	0.025	−0.158	0.208	50.21	0.787	31.1	0.133	−0.575	0.842	36.49	0.712
	Other	7	77.5**	0.109	−0.135	0.352	67.95	0.382	94.3**	−0.122	−1.378	1.134	49.79	0.849	70.9*	−0.169	−0.699	0.361	63.51	0.532
	Overall	13	71.2**	0.009	−0.202	0.221	100	0.930	84.8**	−0.073	−0.611	0.466	100	0.791	54.6*	0.059	−0.477	0.358	100	0.781
Fat yield	Dairy	5	89.7	−0.612	−1.333	0.11	66.95	0.097	3.4	0.069	−0.301	0.439	81.54	0.714	43.4	0.138	−0.266	0.541	78.8	0.503
	Other	2	0	0.305	0.045	0.566	33.05	0.022	0	0.097	−0.681	0.874	18.46	0.808	0	−0.121	−0.899	0.657	21.2	0.761
	Overall	7	87.1	−0.284	−0.752	0.183	100	0.233	0	0.074	−0.26	0.408	100	0.663	0	0.083	−0.275	0.441	100	0.650
Fat content	Dairy	8	0	−0.004	−0.141	0.133	59.94	0.957	0	−0.043	−0.4	0.315	87.26	0.815	0	−0.136	−0.523	0.251	85.3	0.491
	Other	4	83.4**	0.072	−0.389	0.533	40.06	0.760		−0.029	−0.964	0.907	12.74	0.952		−0.036	−0.969	0.896	14.7	0.939
	Overall	12	50.5*	0.042	−0.132	0.217	100	0.634	0	−0.041	−0.375	0.293	100	0.810	0	−0.121	−0.479	0.236	100	0.506
Protein yield	Dairy	2	97.4**	−1.798	−5.394	1.798	64.76	0.327		0.914	−0.001	1.829	100	0.050		0.854	−0.1	1.807	100	0.079
	Other	1		0.27	−0.108	0.648	35.24	0.162												
	Overall	3	95.5**	−0.99	−2.384	0.404	100	0.164		0.914	−0.001	1.829	100	0.050		0.854	−0.1	1.807	100	0.079
Protein content	Dairy	6	0	−0.031	−0.172	0.11	72.2	0.665	0	0	−0.383	0.382	100	1.000	0	−0.031	−0.441	0.379	100	0.881
	Other	2	86.9**	0.373	−0.357	1.104	27.8	0.317												
	Overall	8	60.4*	0.085	−0.137	0.307	100	0.453	0	0	−0.383	0.382	100	1.000	0	−0.031	−0.441	0.379	100	0.881

* $p<0.10$. ** $P<0.01$. n number of publication.

2004; Felenczak et al., 2008), these differences were not significant in other studies (Eenennaam and Medrano, 1991; Micinski et al., 2006; Czerniawska et al., 2011).

A total of 19 studies were used to examine the relationship among the *BLG* genotype and protein content. Although a statistically significant relationship ($P<0.05$) was found between AA vs. AB and AB vs. BB genotypes in all cattle in terms of protein content, the relationship among AA vs. BB genotypes was not significant ($P>0.05$). While a statistically significant relationship ($P<0.05$) was observed among the AA vs. AB genotypes in the dairy subgroup and among the AB vs. BB genotype protein content values in the other subgroup, significant differences were not found among protein content values for the other genotypes examined ($P>0.05$). Based on these results, we conclude that the *BLG* homozygote genotypes are superior and this should be taken into consideration during selective breeding. In other genetic model analyses, the AA genotype was found to be superior in the dairy subgroup using the recessive model; superiority in favor of the BB genotype was just observed in the other subgroup using the dominant model. No significant relationships were found between the protein content values and other genotypes. In the individual studies performed, while some authors found the differences among protein content means in the various *BLG* genotypes significant (Ojala et al., 2004; Felenczak et al., 2008; Mohammadi et al., 2013; Dyman et al., 2015), other authors did not find the differences significant (Eenennaam and Medrano, 1991; Ikonen et al., 1999; Botara et al., 2009; Molee et al., 2015).

Table 5. Results of the meta-analysis on associations among *CSN1S1* genotypes and milk production traits, SMD values, and level of significance.

Traits	Type	BB versus BC						
		n	I^2	SMD	95 %	CI	% Weight	*p*
Daily milk yield	Dairy	4	0	−0.042	−0.415	0.33	28.81	0.824
	Other	4	44.6	0.096	−0.141	0.333	71.19	0.425
	Overall	8	4.9	0.056	−0.144	0.256	100	0.580
Lactation milk yield	Dairy	10	94.9**	0.337	−0.149	0.823	63.04	0.174
	Other	5	33.2	−0.011	−0.194	0.172	36.96	0.906
	Overall	15	92.0**	0.222	−0.085	0.528	100	0.156
Fat yield	Dairy	8	14.1	−0.006	−0.098	0.086	83.98	0.901
	Other	2	0	−0.189	−0.399	0.022	16.02	0.079
	Overall	10	15.2	−0.035	−0.119	0.049	100	0.414
Fat content	Dairy	8	0	0.054	−0.045	0.153	77.94	0.284
	Other	4	0	−0.091	−0.277	0.095	22.06	0.339
	Overall	12	0	0.022	−0.065	0.11	100	0.619
Protein yield	Dairy	4	57.9*	−0.033	−0.231	0.165	82.93	0.744
	Other	1		6.394	5.102	7.627	17.07	0.001
	Overall	5	97.1**	1.114	0.29	1.937	100	0.008
Protein content	Dairy	6	0.2	−0.165	−0.267	−0.063	82.09	0.002
	Other	2	84.8*	−0.39	−1.681	0.901	17.91	0.554
	Overall	8	65.2**	−0.2	−0.426	0.025	100	0.082

* $p<0.10$. ** $P<0.01$. *n* number of publication.

3.3 Analysis *CSN2* genotypes

Few publications have examined *CSN2*. In the analyses to assess the relationship between the genotypes and yield traits, fat yield and AA vs. AB genotypes were found statistically significant only in the other subgroup ($P<0.05$); no significant relationships were observed for any of the other genotypes and traits ($P>0.05$). In the analyses performed using other genetic models, only the fat yield values for genotypes in the other subgroup were found significant when using the recessive and completely overdominant models. The difference in genotype mean values was significant in the other subgroup for lactation milk yield also. The differences among all other genotype means were not significant ($P>0.05$). In some of the individual studies examining *CSN2*, differences among the *CSN2* genotypes were reported to be significant regarding daily milk yield (Heck et al., 2009; Gurcan, 2011; Molee et al., 2015), lactation milk yield (Dogru, 1994; Ikonen et al., 2001; Micinski et al., 2006), protein content (Cardak, 2005; Micinski et al., 2006), fat content (Dogru, 1994; Cardak, 2005), and fat yield (Dogru, 1994). In other studies, these differences in genotypes were not significant for daily milk yield (Dogru, 1994; Gurcan, 2011; Ozdemir and Dogru, 2007), lactation milk yield (Eenennaam and Medrano, 1991; Kaygisiz et al., 1999; Ozdemir and Dogru, 2007), protein content and fat content (Eenennaam and Medrano, 1991; Sekerden et al., 1997; Micinski et al., 2006), and protein yield and fat yield (Eenennaam and Medrano, 1991; Sekerden et al., 1997; Micinski et al., 2006). A study conducted by Ikonen et al. (2001) indicated that *CSN2* BB variants might be useful in direct selection programs for improving milk and fat yield. This finding is further supported by a study conducted by Chung et at. (1996) that reported a highly significant relationship between the *CSN2* AA variant and fat content. However, our meta-analysis results indicate that none of the *CSN2* variants provide an advantage, indicating that they are not particularly useful for improvement programs.

3.4 Analysis of *CSN1S1* genotypes

Few *CSN1S1* studies were suitable for the meta-analyses, so only the relationship between the BB and BC genotypes and yield traits could be examined. Previous studies did not provide sufficient data to assess the other genotypes. According to the results of the meta-analysis performed, highly significant differences ($P<0.01$) were seen between the BB and BC genotype values in terms of protein content in the dairy subgroup and in terms of protein yield in the other subgroup and in all cattle. The differences for other yield traits were not significantly different among other genotypes ($P>0.05$). In the individual studies performed, significant differences among genotypes in terms of fat content, fat yield, protein content, and protein yield were found by a number of authors

(Bovenhuis et al., 1992; Cardak, 2005); in contrast, many researchers reported the relationships between the yield traits and *CSN1S1* genotypes as not significant (Bovenhuis et al., 1992; Ozdemir and Dogru, 2004; Cardak, 2005; Micinski et al., 2006; Gurcan, 2011; Hristov et al., 2013). Our meta-analysis results indicate that *CSN1S1* variants will not provide any advantage in improvement programs for any of the traits examined.

4 Conclusions

In this meta-analysis, the relationships between major milk protein genes and some economic yield traits were analyzed and evaluated according to several genetic models. The meta-analysis demonstrated that the relationships of major milk protein genes with other factors should be examined using the codominant genetic model in general. Significant relationships were determined for the *CSN3* genotypes and fat content and protein content when examined using the meta-analysis. Significant relationships were also determined among the *BLG* genotypes and daily milk yield, fat content, protein yield, and protein content. This suggests that these major genes will be useful for the improvement of the economic yield traits examined and can be used as molecular markers. Furthermore, our analyses generally showed that there were not relationships between the *CSN1S1* and *CSN2* polymorphisms and any of the yield traits examined, and these genes will not be useful as markers for the improvement of traits. Moreover, the meta-analysis performed helped to clarify contradictory studies present in the field.

Data availability. Data sets are not deposited in different repositories and data from a third party were not used. the data is original and users can connect with your site by link.

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