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Research article

PROPORTION OF *PIT-1* GENE HINFI POLYMORPHISM IN DIFFERENT CATTLE BREEDS: A META-ANALYSIS

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The *Pit-1* gene is reported to be one of the strong candidate genes associated with body weight, average daily gain, milk production, and reproductive traits in cattle. This study aimed to determine the pooled frequencies of genotypes and alleles of *Pit-1*/HinfI gene polymorphism in different cattle breeds by meta-analysis and to compare these frequencies between breeds by subgroup analysis. According to the meta-analysis results, the pooled proportion of the A allele was 0.268 (95 % CI: 0.237-0.299), while the pooled proportion of the B allele was 0.733 (95 % CI: 0.702-0.764). High heterogeneity was found between studies for all genotypes and alleles. According to the subgroup analyses, the lowest frequency of the AA genotype was found in the local group (0.051 (95 % CI: 0.023-0.080)), while the highest frequency was observed in the hybrid group (0.011(95 % CI: 0.021-0.189)). The highest frequency of the AB genotype was found in the local breed group (0.444 (95 % CI: 0.377 – 0.510)). The BB genotype frequency was highest in the Simmental breed (0.592 (95 % CI: 0.558-0.627)). The A and B allele frequencies were highest in local breeds (0.279 (95 % CI: 0.225-0.330)) and Simmental breed (0.768 (95 % CI: 0.680-0.856)) respectively. According to the subgroup analyses, it was thought that the distribution of allelic frequencies of Holstein, Simmental, and Brown Swiss breeds, which were bred in the yield direction, was shaped according to their yield traits, while the highest variation was found in local breeds, suggesting that it may be an important indicator of the sustainability of the desired allele in the gene pool in the future.

Keywords: *Pit-1,* HinfI, Dairy cattle, Meta-analysis

INTRODUCTION

In the field of animal breeding, the main motivation for improving any trait in a population is its financial advantage [1]. For quantitative traits, it is difficult to select the best genotypes based on the phenotypic values of animals [2]. In other words, phenotypic values do not always reflect genotypic values, especially the total genotypic values of animals. Using genes related to the economic traits of livestock through

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marker-assisted selection (MAS) can help select animals with the most desirable breeding values [3]. Understanding the relationship between genetic admixture and phenotypic performance is critical for optimizing crossbreeding programs. SNP panels are developed based on allele frequency differences and this information is used in crossbreeding strategies. Knowledge of allele and genotype frequencies will allow optimization of crossbreeding and continuous genetic improvement programs in most cases where pedigree information is not available [4]. In this context, obtaining the most accurate estimates of allele and genotype frequencies of a gene polymorphism within a population is of great importance [3]. Genetic polymorphisms that are significantly associated with certain yield traits are very useful. Detection of polymorphisms in genes related to yield traits and identification of the allele resulting in the phenotype of interest can allow marker-assisted selection [5-7]. Milk yield and its components are quantitative traits controlled by many genes, most of which have small effects. The *Pit-1* gene is one of the candidate genes affecting milk production, protein quality, protein content, body fat percentage, immunity, growth, and development traits in cattle [6]. The *Pit-1* gene, also known as Pituitary-specific positive transcription factor 1 (*Pit-1*), Growth hormone factor 1 (GHF-1), or POU domain, class1 transcription factor 1 (POUF-1), is a gene that synthesizes a 291 amino acid (~33 kD) protein with 6 exons and 5 introns in the centromeric region of chromosome 1 in cattle [8]. *Pit-1* is a member of the POU family or POU domain family, which includes proteins along with OCT-1 (Octamer Transcription Factor) in mammals and the neural Unc-86 in Caenorhabditis elegans [9]. Bovine *Pit-1* is a specific pituitary transcription factor responsible for pituitary development and hormone-secreting gene expression in mammals [10]. It contains a DNA-binding POU domain and, as a transcription factor, can activate its own gene and the expression of target genes including PRL, GH, growth hormone-releasing hormone (GHRH) or somato liberin, the β subunit of thyroid stimulating hormone (β-TSH) and the pituitary β2-Thyroid hormone receptor [11-15]. Renaville *et al.* [16] mentioned that *Pit-1* interferes with pituitary cell differentiation and proliferation in this way. To date, several mutations in the *Pit-1* gene have been identified in the regulation of growth hormone and prolactin. Since it is essential for mammary gland development and thus milk production, the gene encoding *Pit-1* has great potential as a genetic marker for the evaluation of milk production traits [5,17].

Moody *et al.* [18], reported the identification of a restriction fragment length polymorphism for the HinfI enzyme in the bovine *Pit-1* gene. The molecular basis of this polymorphism is a silent mutation (G→A) in exon 6 of the *Pit-1* gene [19]. In some studies in which this polymorphism was examined, it was found to be associated with milk composition and production [8,16,20], growth [6,21,22] and traits in some breeds. It was also found to be associated with body weight in double-muscled Belgian Blue cattle [23], some feeding criteria, and carcass size in the fattening performance of Holstein-Friesian bulls [24], milk yield in Holstein-Friesian [25], fat milk production in Gyr bulls [8], growth traits in Nanyang cattle [26], growth traits in Canchim animals [21] and also German Yellow x Qinchuan beef cattle birth weight and cidago height

[27]. Renaville *et al.* [16], showed that the A allele (for the *Pit-1*/HinfI polymorphism) was superior for milk and protein yield and negatively associated with the fat percentage in dairy cattle. Zwierzchowski *et al.* [28], showed that the A allele of the *Pit-1* locus positively affected milk production traits. In beef cattle, Zhao *et al.* [29] reported that the *Pit-1*/HinfI polymorphism affects growth traits in Angus cattle and may be a candidate gene for use in marker-assisted selection (MAS). Zwierzchowski *et al.* [28] and Dybus *et al.* [17] reported no association between *Pit-1*/HinfI and growth performance and carcass traits of beef cattle. *Pit-1*/HinfI gene polymorphism has a significant place in yield traits, and related studies give different results regarding genotype and allele frequencies. In addition, the genotype and allele frequencies in the population provide preliminary information about the current genetic diversity and future diversity of the population. In this study, it was aimed to determine the pooled ratios of genotypes and alleles of *Pit-1*/HinfI gene polymorphism in different cattle breeds by meta-analysis method and to compare breeds such as Holstein raised for dairy production, Simmental and Brown Swiss raised for combined production, as well as domestic and crossbred breeds by subgroup analysis in terms of these frequencies.

MATERIAL AND METHODS

In this study, the criteria for the studies to be included in the meta-analysis were as follows: the studies used cattle as experimental animals, were associated with the *Pit-1* gene HinfI polymorphism, and genotype and allele frequencies were available or calculable. Literature searching was conducted in Web of Science, Scopus, Google Scholar and PubMed databases using the keywords "*Pit-1* gene", *'POU1F1 gene"*, "HinfI polymorphism", "allele", 'genotype' and "cattle".

Thirty-five proportion data obtained from 27 primary studies regarding the genotype and allele frequencies of *Pit-1*/HinfI polymorphism were used and there were 4933 cows in total. The studies included in the meta-analysis are summarized in Table 1.

The flow diagram for the meta-analysis was created according to PRISMA (Figure 1) [30].

The inverse variance method was used to calculate effect sizes and Cochran's Q statistic and I^2 index were used to determine heterogeneity. Estimation of the true variance between studies was evaluated with the Tau^2 estimator and the Der Simonian Laird method was used for this purpose. In addition to Egger's Linear regression test, publication bias was determined with funnel plots. Duval and Tweedie's Trim and Fill method was used to eliminate funnel plot asymmetry. Subgroup analyses were performed to determine the differences between the breeds in terms of AA, AB and BB genotypes and A and B allele frequencies the subgroups were determined as five groups: Holstein, Simmental, Brown Swiss, hybrid, and local breeds.

Table 1. Studies included in the meta-analysis

Study no	Author	Year	N	AA	AB	BB	A	B	Breed	Breed
1	Zwierzchowski *et al.*, 2002	2002	177	16	56	105	44	133	Holstein Friesian x Polish Black-and-White	Hybrid
2	Dybus *et al.*, 2004	2004	900	47	344	509	219	681	Polish Black-and-White	Local
3	Cosier *et al.*, 2007	2007	76	9	15	52	16	60	Simmental	Simmental
4	Edriss *et al.*, 2008	2008	262	8	118	136	67	195	Holstein Friesian	Holstein Friesian
5	Edriss *et al.*, 2009	2009	268	8	139	121	69	199	Holstein Friesian	Holstein Friesian
6	Jawasreh *et al.*, 2009	2009	45	2	12	31	8	37	Holstein Friesian	Holstein Friesian
7	Misrianti *et al.*, 2010	2010	45	1	20	24	11	34	Holstein Friesian	Holstein Friesian
8	Selvaggi and Dario, 2011	2011	104	15	33	56	31	73	Podolika Cattle	Local
9	Ozdemir, 2012 1	2012	71	10	38	23	29	42	East Anatolian Red	Local
10	Ozdemir, 2012 2	2012	181	7	56	118	36	145	Holstein Friesian	Holstein Friesian
11	Carsai *et al.*, 2012 1	2012	60	0	12	48	6	54	Romanian Black and White	Local
12	Carsai *et al.*, 2012 2	2012	60	0	30	30	15	45	Romanian Grey Steppe	Local
13	Aytekin and Boztepe, 2013	2013	301	35	155	111	113	188	Brown Swiss	Brown Swiss
14	Trakovicka *et al.*, 2013	2013	353	19	138	196	88	265	Slovak Simmental	Simmental
15	Khaizaran and Al Razem,2014 1	2014	101	52	34	15	69	32	Holstein Friesian	Holstein Friesian
16	Khaizaran and Al Razem, 2014 2	2014	18	3	6	9	6	12	Hybrid	Hybrid
17	Khaizaran and Al Razem, 2014 3	2014	25	1	9	15	6	20	Local	Local
18	Trakovicka *et al.*, 2014	2014	89	5	23	61	17	72	Holstein Friesian	Holstein Friesian
19	Hoseinzadeh *et al.*, 2015	2015	100	6	40	54	26	74	Holstein Friesian	Holstein Friesian
20	Trakovicka *et al.*, 2015	2015	288	15	100	173	65	223	Slovak Simmental	Simmental
21	Ahmadi *et al.*, 2015	2015	57	2	21	34	13	44	Holstein Friesian	Holstein Friesian
22	Chauhan *et al.*, 2015	2015	77	3	24	50	15	62	Sahiwal cattle	Local
23	Bayram *et al.*, 2017	2017	352	62	101	189	113	239	Holstein Friesian	Holstein Friesian
24	Oner *et al.*, 2017	2017	146	8	58	80	37	109	Holstein Friesian	Holstein Friesian
25	Thuy *et al.*, 2018	2018	125	10	34	81	27	98	Holstein Friesian	Holstein Friesian
26	Zabeel *et al.*, 2018	2018	61	5	42	14	26	35	Iraqi Local	Local
27	Gokcan, 2019	2019	52	1	12	39	7	45	Holstein Friesian	Holstein Friesian
28	Zabeel *et al.*, 2019	2019	120	7	84	29	49	71	Iraqi Local	Local
29	Ilie *et al.*, 2021 1	2021	55	6	30	19	21	34	Romanian Brown	Local
30	Ilie *et al.*, 2021 2	2021	82	0	33	49	17	65	Romanian Spotted	Local
31	Aytekin and Bayraktar, 2022 1	2022	50	3	19	27	13	37	Anatolian Black	Local
32	Aytekin and Bayraktar, 2022 2	2022	50	0	9	41	5	45	Brown Swiss	Brown Swiss
33	Aytekin and Bayraktar, 2022 3	2022	50	5	22	23	16	34	Holstein Friesian	Holstein Friesian
34	Aytekin and Bayraktar, 2022 4	2022	50	5	13	32	12	38	Simmental	Simmental
35	Findik and Ozdemir, 2022	2022	82	11	33	38	28	54	Holstein Friesian	Holstein Friesian

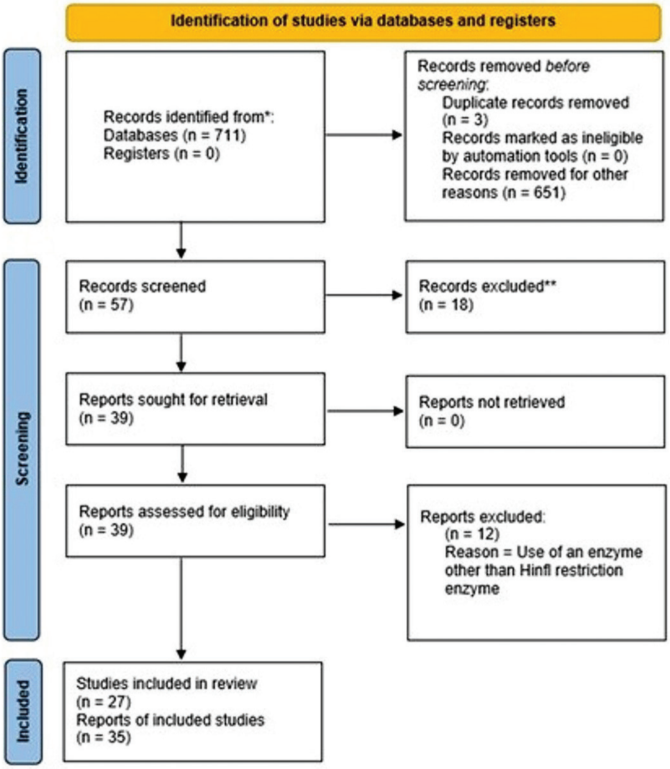


Figure 1. This flow diagram demonstrates the study selection process carried out consistent with the PRISMA 2020 guidelines. It summarizes the number of records identified by database searching, screened, assessed for eligibility, and finally included in the meta-analysis, along with reasons for exclusions.

All analyses were performed with the "*Metaphor*" and "*Meta*" packages in RStudio (Version 2023.06.1+524) software. The significance levels of Cochran's Q statistics were determined as P<0.10, while the significance levels of common effect sizes were accepted as P<0.05.

RESULTS

According to the meta-analysis results, the highest pooled proportion was found for the BB genotype (0.539 (95 % CI: 0.491-0.588)), while the lowest pooled proportion was found for the AA genotype (0.069 (95 % CI: 0.052-0.085)). Also the AB genotype was found (0.378 (95 % CI: 0.340-0.416)). The pooled proportion of the A allele was 0.268 (95 % CI: 0.237-0.299), while the pooled proportion of the B allele was 0.733 (95 % CI: 0.702-0.764). High heterogeneity was found between studies for all genotypes and alleles (Table 2).

Table 2. *Pit-1*/HinfI enzyme pooled genotype and allele frequencies

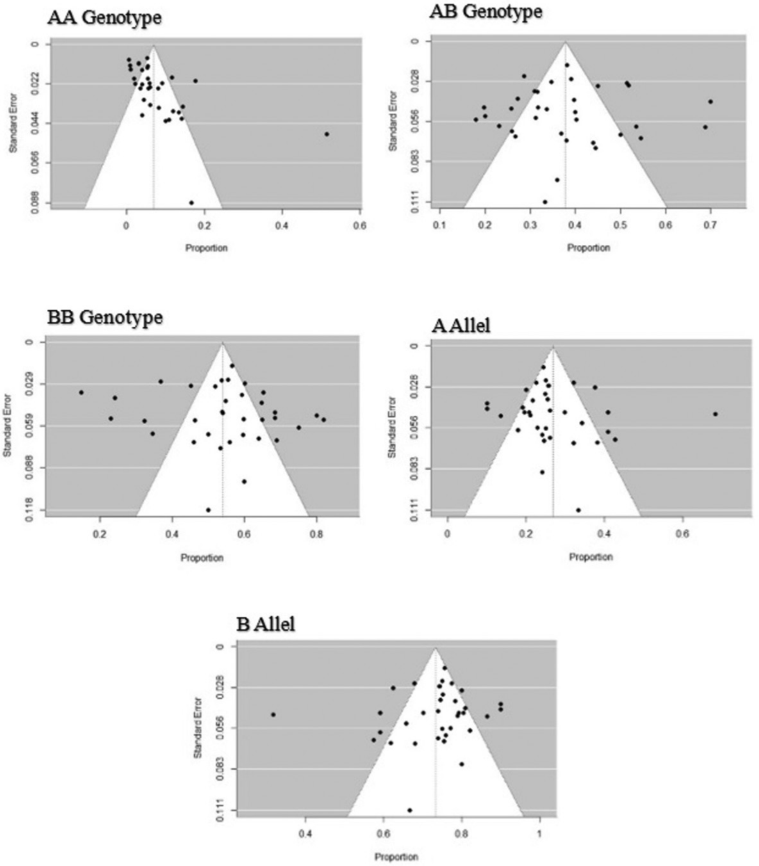
Item	Subgroup	N	Pooled Proportion	95 % CI		Cochran's Q	P Value	Tau^2	I^2
Genotype				**Lower**	**Upper**				
	AA	35	0.069	0.052	0.085	242.70	<0.001	0.002	85.99
	AB	35	0.378	0.340	0.416	249.81	<0.001	0.011	86.39
	BB	35	0.539	0.491	0.588	404.66	<0.001	0.018	91.60
Alleles									
	A	35	0.268	0.237	0.299	196.51	<0.001	0.007	82.70
	B	35	0.733	0.702	0.764	197.01	<0.001	0.007	82.74

According to Egger's linear regression test, publication bias was found in the AA genotype sample (t=3.946, P<0.001) (Table 3). According to Duval and Tweedie's Trim and Fill method, pooled AA genotype frequency was 0.034 [95 % CI: 0.002 – 0.066] with the addition of 13 missing studies (Table 3).

Table 3. Publication bias test results for *Pit-1*/HinfI enzyme study samples

Item	Subgroup	Egger's linear regression test results			
		Intercept	**95 % CI**	**t**	**P value**
Genotype					
	AA	3.139	1.58-4.70	3.946	<0.001
	AB	-0.151	-2.36-2.06	-0.134	0.895
	BB	0.661	-2.18-3.50	0.457	0.651
Alleles					
	A	0.717	-1.2-2.64	0.731	0.470
	B	-0.672	-2.6-1.26	-0.682	0.500

Funnel plots of the study samples for all genotype and allele frequencies are given in Figure 2.


AA Genotype

AB Genotype

BB Genotype

A Allel

B Allel

Figure 2. The funnel plots indicate the distribution of individual study estimates for genotype (AA, AB, BB) and allele (A and B) frequencies in relation to their standard errors.

According to the subgroup analyses, the lowest frequency of the AA genotype was found in the local group (0.051 (95 % CI: 0.023-0.080)), while the highest frequency was observed in the hybrid group, which included two studies (0.011(95 % CI: 0.021-0.189)). The highest frequency of the AB genotype was found in the local breed group (0.444 (95 % CI: 0.377 – 0.510)); the lowest was found in the Simmental breed (0.304 (95 % CI: 0.196-0.412)). The BB genotype frequency was highest in the Simmental breed (0.592 (95 % CI: 0.558-0.627)) and lowest in the local breed group (0.492 (95 % CI: 0.409-0.576)). The A allele frequency was highest in local breeds (0.279 (95 % CI: 0.225-0.330)); and the lowest in other Simmental breeds (0.232 (95 % CI: 0.144-0.320)). The B allele frequency was highest in the Simmental breed (0.768 (95 % CI: 0.680-0.856)) and lowest in local breeds (0.723 (95 % CI: 0.669-0.856)). Significant differences were found between races for all genotype and allele frequencies (P<0.001) (Table 4).

Table 4. Subgroup analyses of *Pit-1*/HinfI enzyme common genotype and allele frequencies according to breeds

Breeds	N	Pooled Ratio (95% CI)	Tau^{2} Index	Tau Index
AA Genotype				
Brown Swiss	2	0.056(0.000-0.119)	0.0018	0.0427
Holstein Friesian	15	0.077(0.052-0.102)		
Simmental	4	0.074(0.025-0.123)		
Local	12	0.051(0.023-0.080)		
Hybrid	2	0.105(0.021-0.189)		
Cochran's Q Statistics=2.74, df=4, p=0.602				
AB Genotype				
Brown Swiss	2	0.362(0.208-0.515)	0.0105	0.1023
Holstein Friesian	15	0.359(0.301-0.416)		
Simmental	4	0.304(0.196-0.412)		
Local	12	0.444(0.377-0.510)		
Hybrid	2	0.322(0.150-0.494)		
Cochran's Q Statistics=28.45, df=4, p<0.001				
BB Genotype				
Brown Swiss	2	0.582(0.385-0.779)	0.0184	0.1357
Holstein Friesian	15	0.545(0.472-0.619)		
Simmental	4	0.617(0.477-0.758)		
Local	12	0.492(0.409-0.576)		
Hybrid	2	0.558(0.341-0.775)		
Cochran's Q Statistics=2.65, df=3, p=0.618				
A Allele				
Brown Swiss	2	0.247(0.125-0.369)	0.0065	0.0807
Holstein Friesian	15	0.271(0.225-0.318)		
Simmental	4	0.232(0.144-0.320)		
Local	12	0.279(0.225-0.330)		
Hybrid	2	0.273(0.129-0.417)		
Cochran's Q Statistics=0.96, df=4, p=0.916				
B Allele				
Brown Swiss	2	0.753(0.631-0.876)	0.0065	0.0808
Holstein Friesian	15	0.729(0.682-0.775)		
Simmental	4	0.768(0.680-0.856)		
Local	12	0.723(0.669-0.777)		
Hybrid	2	0.727(0.583-0.871)		
Cochran's Q Statistics=0.89, df=3, p=0.927				

df= degree of freedom, **C.I.:** Confidence Interval, **Tau^{2} Index:** Variance between studies

Forest plots for AA, AB and BB genotypes and A and B alleles are given in Figure 3., Figure 4., Figure 5., Figure 6. and Figure 7., in the Supplementary Information, respectively.

DISCUSSION

One of the candidate genes associated with traits such as milk yield and its components in cattle is the *Pit-1* gene. There are some studies in the literature evaluating this relationship. Renaville *et al.* [16], examined *Pit-1*/HinfI polymorphism in Italian Holstein-Fresian bulls and also milk composition traits and body conformation traits that could be inherited by daughters of bulls belonging to the genotypes obtained by two different statistical models. According to the results obtained, it was reported that the A allele may be positively associated with milk and protein content and negatively associated with fat percentage. However, it has been suggested that this result should be confirmed with a larger sample size in this study. According to some studies referenced in this article; Parmentier *et al.* [11] reported that the A allele may be associated with milk yield and protein percentage in the articles discussed in the literature [31]. Zierzchowski *et al.* [28] reported that both genotypes (AA, AB) with A allele at the *Pit-1* locus of Polish-Black and White cattle positively affected all milk quantity and composition traits examined. In addition, similar results were found in other references [8,9,32]. Sadeghi *et al.* [33] reported that milk fat and milk protein percentages of the related polymorphism in Iranian Holstein cattle were lowest in the AA genotype and had a statistically significant difference from other genotypes.

According to the results obtained in our study, the highest pooled genotypic proportion was found in the BB genotype (0.539), while the proportion of the B allele (0.733) was higher than the A allele (0.268). Similarly, Zwierzchowski *et al.* [28] reported that the highest frequency was determined in the BB genotype (0.590). Dybus *et al.* [17] calculated the frequency of the B allele as higher (0.757).

In the meta-analysis, the BB genotype and B allele frequencies were higher in Simmental cows (0.617 and 0.768, respectively) than in Brown Swiss cows (0.582 and 0.753, respectively). Aytekin and Bayraktar [6] determined that the BB genotype frequency and B allele of Simmental cows were higher than Holstein cows. Indeed, similar results were obtained in our study.

Trakovichka *et al.* [5] reported that the highest genotype was BB (0.69) and the B allele frequency was 0.81 in Holstein breed cows. Trakovicka *et al.* [34] reported that the observed B allele frequency was 0.774 in Slovak Simmental cattle (n=288). It was also reported that the frequency of the BB genotype was 0.601. In our study, it was also determined that the BB genotype was at the lowest level in local breeds instead of Holstein, Simental and Brown Swiss breeds which are bred in the combined yield direction. In a study conducted by Ilie *et al.* [35] in the Romanian Simmental breed, it was reported that the B allele frequency was higher than the A allele. In the study reported by Korkmaz and Akyüz in Simmental cattle, it was reported that the AA genotype was not found [36]. It was reported that the BB genotype frequency was 0.74 in Simmental cattle. Jawasreh *et al.* [37] conducted a polymorphism study with Holstein cattle (n=81) and found that the frequency of the B allele was higher than A. In the study conducted by Öner *et al.* [38], in Holstein-Fresian heifers (n=160), the frequencies of the A and B alleles were determined as 25.34 and 74.66, respectively. Genotypic frequencies were determined as 5.48, 39.73, and 54.79. Thuy *et al.* [39] determined the A allele frequency as 0.216 and AA, AB, and BB genotypes as 0.08, 0.27, and 0.64 in Holstein Friesian cattle (n=125). In the study conducted by Bayram *et al.* [40] with Holstein cattle (n=352), the B allele frequency was determined as 0.68. Genotypes AA, AB, and BB were reported as 17.62, 28.69 and 53.69 %, respectively. In the study reported by Gökcan [41] with Holstein cattle (n=52), AA, AB, and BB genotype frequencies were 0.019, 0.231, and 0.750, and A and B allele frequencies were 0.135 and 0.865, respectively. Fındık and Özdemir [42] reported that AA, AB, and BB genotype frequencies were determined as 13.4 %, 40.2 %, and 46.3 %, respectively, in Holstein calves (n=100). In all the studies mentioned above, the B allele frequency was reported to be higher than the A allele, and as a result of the meta-analysis, it was determined that the B allele frequency was generally higher.

For the other breeds subgroup, the BB genotype had the highest frequency (0.414), the AA genotype had the lowest (0.073). In the study conducted by Ilie *et al.* [35] in Romanian Spotted (n=137) and Romanian Brown (n=82) cattle breeds, it was reported that the AA genotype was very low in the Romanian Brown breed and AA genotype was never observed in the spotted breed. In a study conducted by Pytlewski *et al.* [15] with Polish Black and White Holstein-Fresian cattle (n=1024 cattle and n=3663 offspring), A allele frequency was found to be 0.205. Genotypes were reported as AA, AB, BB, 0.04, 0.31, and 0.63, respectively. In subgroup analyses, similar results were obtained with the general analyses in determining allelic frequencies. The frequency of the A allele in the subgroups varied between 0.232 and 0.279.

Aytekin and Boztepe [43] conducted a study on Brown Swiss cattle (n=301) and found that A and B allele frequencies were 0.374 and 0.626, respectively. In the subgroup analysis performed in our study, AA, AB, BB genotypes were observed as 0.05, 0.362, 0.582, while A and B alleles were 0.247, 0.753, respectively.

Chauhan *et al.* [44] conducted a study with Sahiwal cattle (n=77) and found that AA, AB, and BB genotypes were 3.89 %, 31.16 %, and 64.98 %, respectively. A and B allele frequencies were 19.48 % and 80.51 %, respectively. Selvaggi *et al.* [45] reported that the frequency of the B allele was 70 % in Podolica cattle (n=104) (44). Grossi *et al.* [46] reported that A and B allele frequencies were 0.21 and 0.79, and genotype frequencies were AA, AB, BB, 0.06, 0.30, and 0.64, respectively, in their study conducted on Canchim cattle. Gritsienko *et al.* [47] reported that in Ukranian dairy cows (Ukranian Red n=32, Ukranian Black-speckled n=32, Ukranian Red-speckled n=28), it was determined that AA genotype had the lowest frequency compared to other genotypes. Doosti *et al.* [48] found the frequency of the B allele to be 0.25 in a study on indigenous Iranian cattle. In contrast to this information, Tang *et al.* [22] found that B allele frequencies were higher than A allele frequencies in Chinese native cattle breeds (Nanyang cattle, Qinchuan cattle, Jiaxianhong cattle, Luxi cattle and Holstein cattle. In the study reported by Zabel *et al.* [49] on domestic breeds (n=61), the frequency of the A allele was reported as 0.57. However, it was reported that it should be confirmed with more samples. In the study by Zabeel *et al.* [49] which examined the relationship of the related polymorphism with some blood parameters in native breed cattle, the frequency of the A allele was reported as 0.41 and the frequency of the B allele was reported as 0.59. The frequencies of AA, AB, and BB genotypes were reported as 0.06, 0.70, and 0.24, respectively. As a result of the meta-subgroup analysis, AA, AB and BB genotypes in local groups were 0.051 (95 % CI: 0.023-0.080), 0.444 (95 % CI: 0.377-0.510) and 0.492 (95 % CI: 0.409-0.576) A allele frequencies were 0.279 (095 % CI:.225-0.330), 0.723 (95 % CI: 0.669-0.777). According to the results obtained, it was determined that the variation was mostly observed in local breeds.

As a result, when the pooled genotype and allele frequencies of all studies were analyzed, it was found that AA, AB and BB genotype frequencies were 0.069, 0.378, 0.539 and A allele frequency (0.268) was lower than B allele frequency (0.733). However, when subgroup analyses were investigated, it was determined that there was a statistically significant difference between the subgroups according to Cohran Q analysis in the AB genotype frequency, and the frequency of native breeds had the highest frequency of 0.444 compared to the other groups. The low heterozygosity in Holstein, Simental and Brown Swiss breeds may be related to the selection of yield-oriented characters. In addition, it was thought that the high B allele in Simmental breed may be related to the fact that it was subjected to selection as a combined meat and dairy breed. In some of the literature reviewed, the association of the A allele with milk quantity and protein amount was found especially in Holstein breed, but it was also reported that these relationships were not found in some later studies. In addition, the number of samples belonging to the populations examined, the fact that the population was grown in a limited area, artificial insemination, selection and the differences in the genetic composition of the animals may be effective at the population level were thought to be among the limitations of the study. Especially the fact that quantitative characters are under the influence of many genes and the Pit-I/HinfI allele may make it difficult to interpret the phenotype-genotype relationship clearly according to the literatures examined. The meta-analysis study revealed allelic and genotypic variation among breeds in the general and subgroup analyses of populations. The highest variation was found in local breeds. The fact that the variation is high in local breeds may be important for taking the necessary measures to ensure the sustainability of the desired allele. The results obtained provide valuable information about the gene pools of populations for researchers who will plan phenotype-genotype association studies related to the studied polymorphism.

CONCLUSION

Literature review and meta-analysis results demonstrated that the highest frequency genotype of Pit-HinfI polymorphism was generally BB and the highest frequency allele was B allele. According to the subgroup analyses, it was thought that the distribution of allelic frequencies of Holstein, Simental, and Brown Swiss breeds, which were bred for yield, was shaped according to their yield traits, while the highest variation was found in local breeds, suggesting that it may be an important indicator of the sustainability of the gene pool in the future. The study provides valuable information on the genotypic and allelic frequency of the relevant allele in the population, both in terms of pooled and subgroups.

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Author contributions

EÇG designed the study. EÇG performed the literature review. EÇG and EGA wrote the article. EÇG and EGA reviewed and revised the manuscript. All authors have read and accepted the final version of the manuscript.

Declaration of conflicting interests

The authors declare that they have no conflicts of interest.

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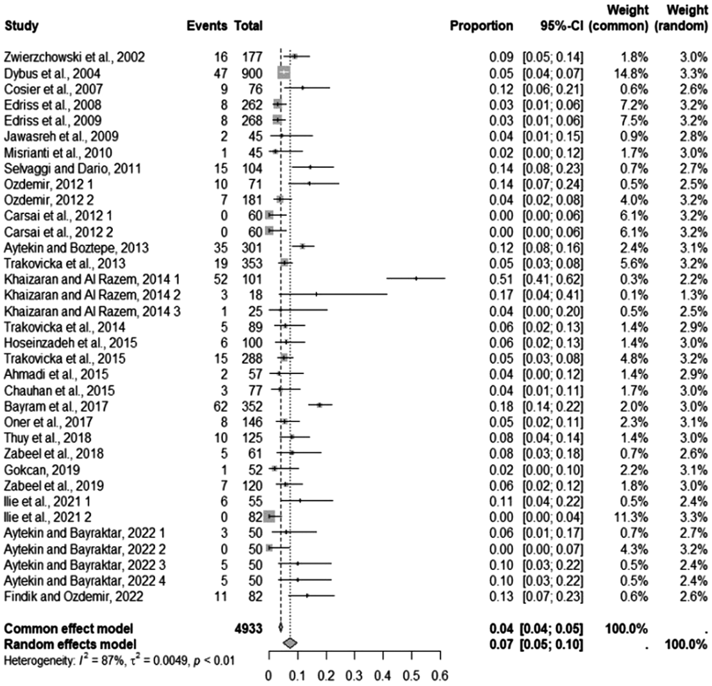
UDEO POLIMORFIZMA GENA *PIT-1 HINFI* KOD RAZLIČITIH RASA GOVEDA: META-ANALIZA

Elif ÇELİK GÜRBULAK , Esma Gamze AKSEL

Gen *Pit-1* se smatra jednim od važnih kandidatskih gena povezanih sa telesnom težinom, prosečnim dnevnim prirastom, proizvodnjom mleka i reproduktivnim osobinama goveda. Cilj ove studije je bio da se odrede zbirne frekvencije genotipova i alela polimorfizma gena *Pit-1*/HinfI kod različitih rasa goveda meta-analizom i da se uporede ove frekvencije između rasa analizom podgrupa. Prema rezultatima meta-analize, zbirni udeo alela A bio je 0,268 (95 % CI: 0,237-0,299), dok je zbirni udeo alela B bio 0,733 (95 % CI: 0,702-0,764). Utvrđena je velika heterogenost između studija za sve genotipove i alele. Prema analizama podgrupa, najniža učestalost genotipa AA pronađena je u lokalnoj grupi (0,051 (95 % CI: 0,023-0,080)), dok je najveća učestalost primećena u hibridnoj grupi (0,011 (95 % CI: 0,021-0,189)). Najveća učestalost genotipa AB pronađena je u lokalnoj rasnoj grupi (0,444 (95 % CI: 0,377-0,510)). Učestalost BB genotipa bila je najveća kod simentalske rase (0,592 (95 % CI: 0,558-0,627)). Učestalosti alela A i B bile su najveće kod lokalnih rasa (0,279 (95 % CI: 0,225-0,330)) i simentalske rase (0,768 (95 % CI: 0,680-0,856)). Prema analizama podgrupa, smatralo se da je distribucija alelnih frekvencija rasa holštajn, simental i smeđe švajcarske krave, koje su uzgajane u pravcu prinosa, oblikovana prema njihovim osobinama prinosa, dok je najveća varijacija pronađena kod lokalnih rasa, što sugeriše da bi to mogao biti važan pokazatelj održivosti željenog alela u genskom fondu u budućnosti.

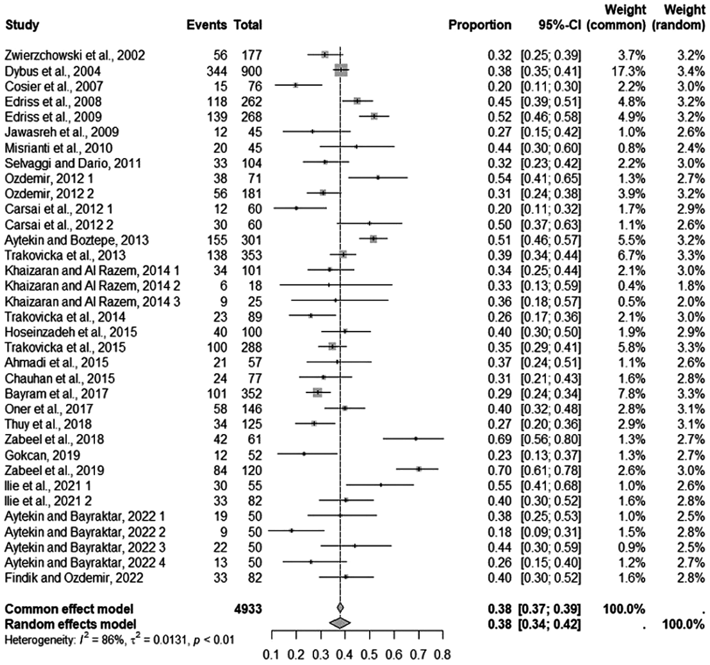
Supplementary files



Study	Events	Total	Proportion	95%-CI	Weight (common)	Weight (random)
Zwierzchowski et al., 2002	16	177	0.09	[0.05; 0.14]	1.8%	3.0%
Dybus et al., 2004	47	900	0.05	[0.04; 0.07]	14.8%	3.3%
Cosier et al., 2007	9	76	0.12	[0.06; 0.21]	0.6%	2.6%
Edriss et al., 2008	8	262	0.03	[0.01; 0.06]	7.2%	3.2%
Edriss et al., 2009	8	268	0.03	[0.01; 0.06]	7.5%	3.2%
Jawasreh et al., 2009	2	45	0.04	[0.01; 0.15]	0.9%	2.8%
Misrianti et al., 2010	1	45	0.02	[0.00; 0.12]	1.7%	3.0%
Selvaggi and Dario, 2011	15	104	0.14	[0.08; 0.23]	0.7%	2.7%
Ozdemir, 2012 1	10	71	0.14	[0.07; 0.24]	0.5%	2.5%
Ozdemir, 2012 2	7	181	0.04	[0.02; 0.08]	4.0%	3.2%
Carsai et al., 2012 1	0	60	0.00	[0.00; 0.06]	6.1%	3.2%
Carsai et al., 2012 2	0	60	0.00	[0.00; 0.06]	6.1%	3.2%
Aytekin and Boztepe, 2013	35	301	0.12	[0.08; 0.16]	2.4%	3.1%
Trakovicka et al., 2013	19	353	0.05	[0.03; 0.08]	5.6%	3.2%
Khaizaran and Al Razem, 2014 1	52	101	0.51	[0.41; 0.62]	0.3%	2.2%
Khaizaran and Al Razem, 2014 2	3	18	0.17	[0.04; 0.41]	0.1%	1.3%
Khaizaran and Al Razem, 2014 3	1	25	0.04	[0.00; 0.20]	0.5%	2.5%
Trakovicka et al., 2014	5	89	0.06	[0.02; 0.13]	1.4%	2.9%
Hoseinzadeh et al., 2015	6	100	0.06	[0.02; 0.13]	1.4%	3.0%
Trakovicka et al., 2015	15	288	0.05	[0.03; 0.08]	4.8%	3.2%
Ahmadi et al., 2015	2	57	0.04	[0.00; 0.12]	1.4%	2.9%
Chauhan et al., 2015	3	77	0.04	[0.01; 0.11]	1.7%	3.0%
Bayram et al., 2017	62	352	0.18	[0.14; 0.22]	2.0%	3.0%
Oner et al., 2017	8	146	0.05	[0.02; 0.11]	2.3%	3.1%
Thuy et al., 2018	10	125	0.08	[0.04; 0.14]	1.4%	3.0%
Zabeel et al., 2018	5	61	0.08	[0.03; 0.18]	0.7%	2.6%
Gokcan, 2019	1	52	0.02	[0.00; 0.10]	2.2%	3.1%
Zabeel et al., 2019	7	120	0.06	[0.02; 0.12]	1.8%	3.0%
Ilie et al., 2021 1	6	55	0.11	[0.04; 0.22]	0.5%	2.4%
Ilie et al., 2021 2	0	82	0.00	[0.00; 0.04]	11.3%	3.3%
Aytekin and Bayraktar, 2022 1	3	50	0.06	[0.01; 0.17]	0.7%	2.7%
Aytekin and Bayraktar, 2022 2	0	50	0.00	[0.00; 0.07]	4.3%	3.2%
Aytekin and Bayraktar, 2022 3	5	50	0.10	[0.03; 0.22]	0.5%	2.4%
Aytekin and Bayraktar, 2022 4	5	50	0.10	[0.03; 0.22]	0.5%	2.4%
Findik and Ozdemir, 2022	11	82	0.13	[0.07; 0.23]	0.6%	2.6%
Common effect model		**4933**	**0.04**	**[0.04; 0.05]**	**100.0%**	**.**
Random effects model			**0.07**	**[0.05; 0.10]**	**.**	**100.0%**

Heterogeneity: $I^2 = 87\%$, $\tau^2 = 0.0049$, $p < 0.01$

Figure 3.



Study	Events	Total	Proportion	95%-CI	Weight (common)	Weight (random)
Zwierzchowski et al., 2002	56	177	0.32	[0.25; 0.39]	3.7%	3.2%
Dybus et al., 2004	344	900	0.38	[0.35; 0.41]	17.3%	3.4%
Cosier et al., 2007	15	76	0.20	[0.11; 0.30]	2.2%	3.0%
Edriss et al., 2008	118	262	0.45	[0.39; 0.51]	4.8%	3.2%
Edriss et al., 2009	139	268	0.52	[0.46; 0.58]	4.9%	3.2%
Jawasreh et al., 2009	12	45	0.27	[0.15; 0.42]	1.0%	2.6%
Misrianti et al., 2010	20	45	0.44	[0.30; 0.60]	0.8%	2.4%
Selvaggi and Dario, 2011	33	104	0.32	[0.23; 0.42]	2.2%	3.0%
Ozdemir, 2012 1	38	71	0.54	[0.41; 0.65]	1.3%	2.7%
Ozdemir, 2012 2	56	181	0.31	[0.24; 0.38]	3.9%	3.2%
Carsai et al., 2012 1	12	60	0.20	[0.11; 0.32]	1.7%	2.9%
Carsai et al., 2012 2	30	60	0.50	[0.37; 0.63]	1.1%	2.6%
Aytekin and Boztepe, 2013	155	301	0.51	[0.46; 0.57]	5.5%	3.2%
Trakovicka et al., 2013	138	353	0.39	[0.34; 0.44]	6.7%	3.3%
Khaizaran and Al Razem, 2014 1	34	101	0.34	[0.25; 0.44]	2.1%	3.0%
Khaizaran and Al Razem, 2014 2	6	18	0.33	[0.13; 0.59]	0.4%	1.8%
Khaizaran and Al Razem, 2014 3	9	25	0.36	[0.18; 0.57]	0.5%	2.0%
Trakovicka et al., 2014	23	89	0.26	[0.17; 0.36]	2.1%	3.0%
Hoseinzadeh et al., 2015	40	100	0.40	[0.30; 0.50]	1.9%	2.9%
Trakovicka et al., 2015	100	288	0.35	[0.29; 0.41]	5.8%	3.3%
Ahmadi et al., 2015	21	57	0.37	[0.24; 0.51]	1.1%	2.6%
Chauhan et al., 2015	24	77	0.31	[0.21; 0.43]	1.6%	2.8%
Bayram et al., 2017	101	352	0.29	[0.24; 0.34]	7.8%	3.3%
Oner et al., 2017	58	146	0.40	[0.32; 0.48]	2.8%	3.1%
Thuy et al., 2018	34	125	0.27	[0.20; 0.36]	2.9%	3.1%
Zabeel et al., 2018	42	61	0.69	[0.56; 0.80]	1.3%	2.7%
Gokcan, 2019	12	52	0.23	[0.13; 0.37]	1.3%	2.7%
Zabeel et al., 2019	84	120	0.70	[0.61; 0.78]	2.6%	3.0%
Ilie et al., 2021 1	30	55	0.55	[0.41; 0.68]	1.0%	2.6%
Ilie et al., 2021 2	33	82	0.40	[0.30; 0.52]	1.6%	2.8%
Aytekin and Bayraktar, 2022 1	19	50	0.38	[0.25; 0.53]	1.0%	2.5%
Aytekin and Bayraktar, 2022 2	9	50	0.18	[0.09; 0.31]	1.5%	2.8%
Aytekin and Bayraktar, 2022 3	22	50	0.44	[0.30; 0.59]	0.9%	2.5%
Aytekin and Bayraktar, 2022 4	13	50	0.26	[0.15; 0.40]	1.2%	2.7%
Findik and Ozdemir, 2022	33	82	0.40	[0.30; 0.52]	1.6%	2.8%
Common effect model		**4933**	**0.38**	**[0.37; 0.39]**	**100.0%**	**.**
Random effects model			**0.38**	**[0.34; 0.42]**	**.**	**100.0%**

Heterogeneity: $I^2 = 86\%$, $\tau^2 = 0.0131$, $p < 0.01$

Figure 4.

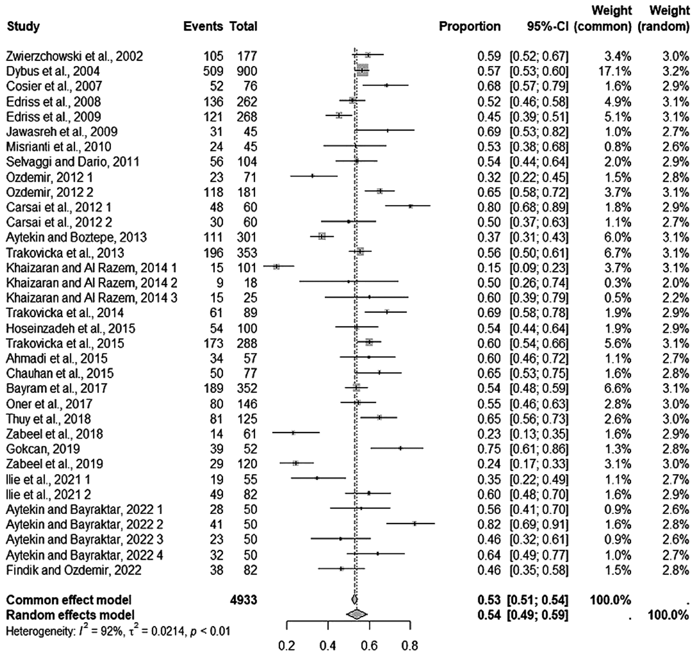


Figure 5.

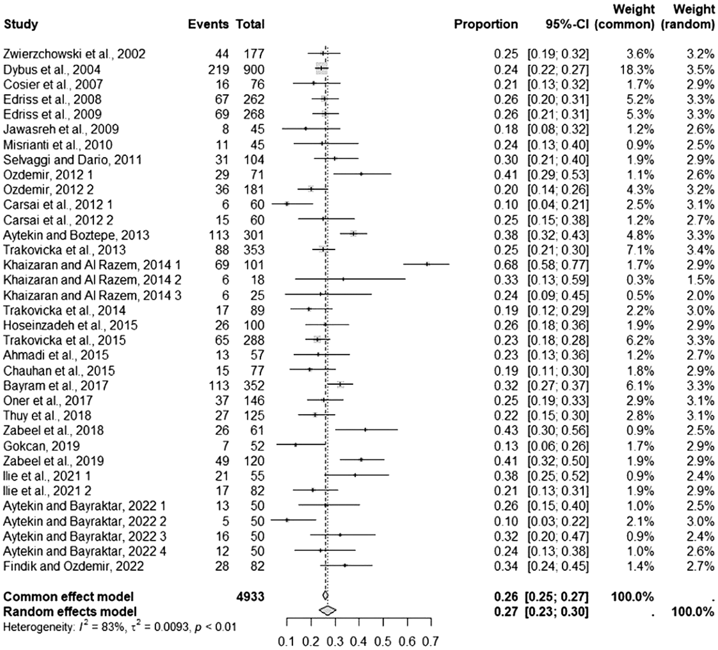
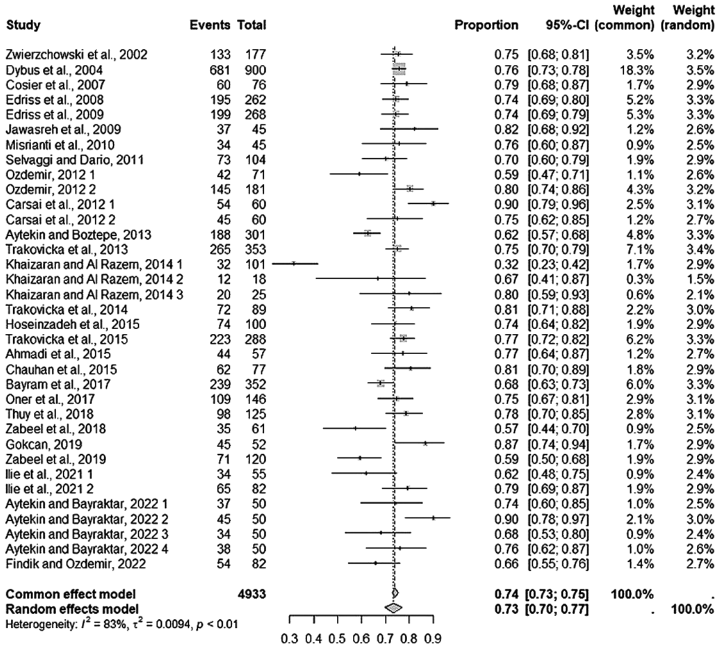


Figure 6.



Study	Events	Total	Proportion	95%-CI	Weight (common)	Weight (random)
Zwierzchowski et al., 2002	133	177	0.75	[0.68; 0.81]	3.5%	3.2%
Dybus et al., 2004	681	900	0.76	[0.73; 0.78]	18.3%	3.5%
Cosier et al., 2007	60	76	0.79	[0.68; 0.87]	1.7%	2.9%
Edriss et al., 2008	195	262	0.74	[0.69; 0.80]	5.2%	3.3%
Edriss et al., 2009	199	268	0.74	[0.69; 0.79]	5.3%	3.3%
Jawasreh et al., 2009	37	45	0.82	[0.68; 0.92]	1.2%	2.6%
Misrianti et al., 2010	34	45	0.76	[0.60; 0.87]	0.9%	2.5%
Selvaggi and Dario, 2011	73	104	0.70	[0.60; 0.79]	1.9%	2.9%
Ozdemir, 2012 1	42	71	0.59	[0.47; 0.71]	1.1%	2.6%
Ozdemir, 2012 2	145	181	0.80	[0.74; 0.86]	4.3%	3.2%
Carsai et al., 2012 1	54	60	0.90	[0.79; 0.96]	2.5%	3.1%
Carsai et al., 2012 2	45	60	0.75	[0.62; 0.85]	1.2%	2.7%
Aytekin and Boztepe, 2013	188	301	0.62	[0.57; 0.68]	4.8%	3.3%
Trakovicka et al., 2013	265	353	0.75	[0.70; 0.79]	7.1%	3.4%
Khaizaran and Al Razem, 2014 1	32	101	0.32	[0.23; 0.42]	1.7%	2.9%
Khaizaran and Al Razem, 2014 2	12	18	0.67	[0.41; 0.87]	0.3%	1.5%
Khaizaran and Al Razem, 2014 3	20	25	0.80	[0.59; 0.93]	0.6%	2.1%
Trakovicka et al., 2014	72	89	0.81	[0.71; 0.88]	2.2%	3.0%
Hoseinzadeh et al., 2015	74	100	0.74	[0.64; 0.82]	1.9%	2.9%
Trakovicka et al., 2015	223	288	0.77	[0.72; 0.82]	6.2%	3.3%
Ahmadi et al., 2015	44	57	0.77	[0.64; 0.87]	1.2%	2.7%
Chauhan et al., 2015	62	77	0.81	[0.70; 0.89]	1.8%	2.9%
Bayram et al., 2017	239	352	0.68	[0.63; 0.73]	6.0%	3.3%
Oner et al., 2017	109	146	0.75	[0.67; 0.81]	2.9%	3.1%
Thuy et al., 2018	98	125	0.78	[0.70; 0.85]	2.8%	3.1%
Zabeel et al., 2018	35	61	0.57	[0.44; 0.70]	0.9%	2.5%
Gokcan, 2019	45	52	0.87	[0.74; 0.94]	1.7%	2.9%
Zabeel et al., 2019	71	120	0.59	[0.50; 0.68]	1.9%	2.9%
Ilie et al., 2021 1	34	55	0.62	[0.48; 0.75]	0.9%	2.4%
Ilie et al., 2021 2	65	82	0.79	[0.69; 0.87]	1.9%	2.9%
Aytekin and Bayraktar, 2022 1	37	50	0.74	[0.60; 0.85]	1.0%	2.5%
Aytekin and Bayraktar, 2022 2	45	50	0.90	[0.78; 0.97]	2.1%	3.0%
Aytekin and Bayraktar, 2022 3	34	50	0.68	[0.53; 0.80]	0.9%	2.4%
Aytekin and Bayraktar, 2022 4	38	50	0.76	[0.62; 0.87]	1.0%	2.6%
Findik and Ozdemir, 2022	54	82	0.66	[0.55; 0.76]	1.4%	2.7%
Common effect model		**4933**	**0.74**	**[0.73; 0.75]**	**100.0%**	.
Random effects model			**0.73**	**[0.70; 0.77]**	.	**100.0%**

Heterogeneity: $I^2 = 83\%$, $\tau^2 = 0.0094$, $p < 0.01$

Figure 7.

Figure 3-7. The figures demonstrate the pooled and individual study estimates of the frequences of the AA, AB, and BB genotypes, and the A and B alleles, respectively, of the *Pit-1*/HinfI gene polymorphism in various cattle breeds. Each horizontal line represents the 95 % confidence interval for a single study, while the diamond indicates the overall pooled estimate. The size of the squares reflects the weight of each study in the meta-analysis.