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ORIGINAL RESEARCH

Relationships between polymorphisms of growth hormone, leptin and myogenic factor 5 genes with some milk yield traits in Holstein dairy cows

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This study was conducted to identify gene polymorphisms and to investigate the relationships of polymorphisms with yield and composition of milk from Holstein cows. Significant relationships of growth hormone (GH)*, leptin (*LEP) *and myogenic factor 5* (MYF5) *gene polymorphisms with 305-day milk yield were observed (*$P < 0.01$*). Signal transducers and activators of transcription 5A* (STAT5A) *gene polymorphism did not show any significant relationships with investigated traits (*$P > 0.05$*). With regard to the 305-day milk yield,* GH-*LV,* LEP-*AA and AB and* MYF5-*GG genotypes were found to be superior over the other genotypes. It was concluded based on present findings that* GH*,* LEP *and* MYF5 *genes could be used as candidate genes for milk yield of Holstein cows.*

Keywords Dairy cows, Genetic markers, Milk production, Milk yield.

INTRODUCTION

Polygenetic inheritance is dominant in almost all commercial aspects of stock breeding. Research has been conducted since the beginning of the 1990s to identify the genes designating significant yield components of farm animals (Singh *et al.* 2014). Such studies mostly focused on dairy farming. During the last two decades, there has been an ever-increasing interest in information about the genes relating to various yield components and efforts to use the resulting information in breeding cattle selections (Oikonomou *et al.* 2011). Attempts have been made to identify quantitative trait loci (QTLs) associated with significant quality traits in various livestock species. Using genomic- or marker-assisted selections for quality and production traits, a rapid genetic gain could be achieved in shorter time periods.

A number of candidate genes have been reported to influence milk yield and milk composition. In dairy cows, the *GH*, *STAT5A*, *LEP* and *MYF5* genes have been reported to be candidate genes for milk yield and milk composition (Flisikowski *et al.* 2004; Hradecká *et al.* 2008; Dario and Selvaggi 2011).

Growth hormones play significant roles in udder development and lactation (Hradecká *et al.* 2008). There is a particular interest of researchers in the growth hormone (*GH*) gene on the *Bos taurus* autosome 19th chromosome (BTA19) of cows because of the active role of this gene in lactation. Previous studies reported significant relationships between *GH* gene polymorphisms and milk yield traits (Akyüz *et al.* 2015). In particular, the polymorphism manifested itself with conversion of leucine–valine amino acid on 127th position of 5th exon of the *GH* gene and, with *Alu*I enzyme section, is the most remarkable one for milk and meat yield traits.

STAT5A is an important transcription factor that plays a significant role in several physiological processes (He *et al.* 2012). The gene is located on the 19th chromosome (BTA19) of bovines and plays a role in the expression of the lactoprotein gene of udder epithelium cells. STAT5A, also called mammary gland factor, and the gene encoding the STAT5A protein mediate the tasks of prolactin and growth

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hormones (Oikonomou *et al.* 2011). Just because of its role in milk yield, the *STAT5A* (signal transducers and activators of transcription 5A) gene was considered to be significant marker for yield components such as milk yield and milk composition (Flisikowski *et al.* 2004; Oikonomou *et al.* 2011). Previous researchers have investigated the relationship of polymorphism expressed by *Ava*I enzyme section in the 7th exon of bovine *STAT5A* gene with milk yield components (Flisikowski *et al.* 2004; Dario and Selvaggi 2011).

The leptin hormone is produced by adipocytes and plays significant roles in several physiological processes including regulation of energy balance, fertility and milk production (Liefers *et al.* 2005). A milk yield-related QLT region was reported around the *LEP* (Leptin) gene on the 4th chromosome (BTA4) of bovines (Lindersson *et al.* 1998). It was also reported that a polymorphism in the 2nd intron of the bovine *LEP* gene might be related to milk yield and quality (Liefers *et al.* 2002; Komisarek *et al.* 2005). In later studies, *LEP* gene was indicated as a candidate gene to be used in marker-assisted selections for significant yield traits of dairy cows (Liefers *et al.* 2005).

The myogenic determination (*MyoD*) gene family is responsible for the development and differentiation of muscle cells. Myogenic factor 5 (*MYF5*) is a member of that family, and the gene encoding this factor is located on the 5th chromosome (BTA5) of bovine karyotype (Li *et al.* 2004). Because of its role in muscle cell development, the relationship of the *MYF5* gene with growth and meat quality have been investigated in previous studies and this gene was reported to be a strong candidate gene for these traits (Li *et al.* 2004). On the other hand, three adipose-related chromosomal regions were reported on the BTA5-bearing *MYF5* gene (Seong *et al.* 2011) and thus the *MYF5* gene was indicated to be a candidate gene for adipose (Rogberg-Muñoz *et al.* 2010). Despite the studies into the relationship of the *MYF5* gene with adipose and fat metabolism, there are no studies in the literature on the relationship of the *MYF5* gene with milk yield and milk composition.

This study was conducted to investigate the relationship of *GH*, *STAT5A*, *LEP* and *MYF5* gene polymorphisms with the milk yield and milk composition of Holstein dairy cows with a 305-day lactation in Turkey.

MATERIAL AND METHOD

Animals milking and milk composition

As the animal material of the study, 167 Holstein dairy cows reared in an intensive dairy facility were used; all of the animals were at their second lactation. Cows were routinely milked three times a day (07:00, 15:00, 23:00), and milk yields were recorded with a computerised herd management system. Milk yield for 305-day lactation was determined. For milk composition and quality analyses, a control day was specified in each month and a 50 mL milk sample was taken from the morning milking (07:00) of each animal on that control day. Samples were kept at +4 °C and used in milk composition analyses. Analyses were performed with a Milkana Multi-Test device. Milk economic traits (% fat, % fat-free dry matter, % density, % protein, % lactose and freezing point) were determined.

Polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) genotyping

All blood samples were collected at the postnatal period, and genomic DNA was extracted by the phenol: chloroform: isoamyl alcohol method. The *GH*, *STAT5A*, *LEP*, *SCD* and *MYF5* gene polymorphisms were genotyped using PCR-RFLP. The PCR reaction mixtures of all genes were prepared with a total volume of 25 μL, including 1.5 mM $MgCl_2$, 200 μM dNTP, 5 pmol of forward and reverse primers of each gene, 1 × PCR buffer, 1U Taq polymerase and 50–100 ng DNA.

The PCR protocols for the genes investigated were as follows: for the *GH* gene, 4 min at 94 °C for 40 min, then 40 cycles at 94 °C for 40 s, at 60 °C for 40 s, at 72 °C for 40 s and the final extension at 72 °C for 10 min; for the *STAT5A* gene, predenaturation at 95 °C for 4 min, then 34 cycles at 94 °C for 1 min, at 64 °C for 1 min, at 72 °C for 1 min and final extension at 72 °C for 10 min; for the *LEP* gene, predenaturation at 95 °C for 2 min, then 35 cycles at 94 °C for 1 min, at 55 °C for 1 min, at 72 °C for 1 min and final extension at 72 °C for 15 min; for the *MYF5* gene, predenaturation at 94 °C for 4 min, then 38 cycles at 94 °C for 30 s, at 58 °C for 1 min, at 72 °C for 1 min and final extension at 72 °C for 4 min. The PCR products of all the genes thus obtained were digested by appropriate restriction enzymes. The nucleotide sequences of the specific PCR primers used for standard PCR amplification, restriction enzymes and product sizes are provided in Table 1.

Statistical analyses

Data were checked for normality before the analyses using the UNIVARIATE procedure of SAS v9.0 (SAS Institute, Cary, NC). Milk traits data were analysed with a mixed model using the MIXED procedure of SAS v9.0. The model included fixed effects of sire and genotype, with a random effect of control. Sire had 19 levels and genotype had three or two levels according to genotype of the investigated genes. Control represented the test day on which test records for milk traits were recorded once a month in a lactation year and it had 10 levels.

RESULTS

The agarose electrophoresis patterns of *GH* (a), *STAT5A* (b), *LEP* (c) and *MYF5* (d) and L: DNA ladder (100 bp) are presented in Figure 1; the genotype and allele frequencies of *GH, STAT5A, LEP* and *MYF5* genes are provided in

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Table 1 Primer sequences used in PCR, product size and restriction enzymes.

Gene	*Sequence*	*Product size (bp)*	*Enzyme*	*References*
GH	F:5′-GCTGCTCCTGAGGGCCCTTCG-3′ R:5′-GCGGCGGCACTTCATGACCCT-3′	223	*Alu*I	Schlee *et al.* (1994)
STAT5A	F:5′-CTGCAGGGCTGTTCTGAGAG-3′ R:5′-TGGTACCAGGACTGTAGCACAT-3′	215	*Ava*I	Flisikowski *et al.* (2004)
LEP	F:5′-TGGAGTGGCTTGTTATTTTCTTCT-3′ R:5′-GTCCCCGCTTCTGGCTACCTAACT-3′	422	*Sau3*AI	Liefers *et al.* (2002)
MYF5	F:5′-AGAGCAGCAGTTTTGACAGC-3′ R:5′-GCAATCCAAGCTGGATAAGG-3′	490	*Taq*I	Şahin and Akyüz (2017)

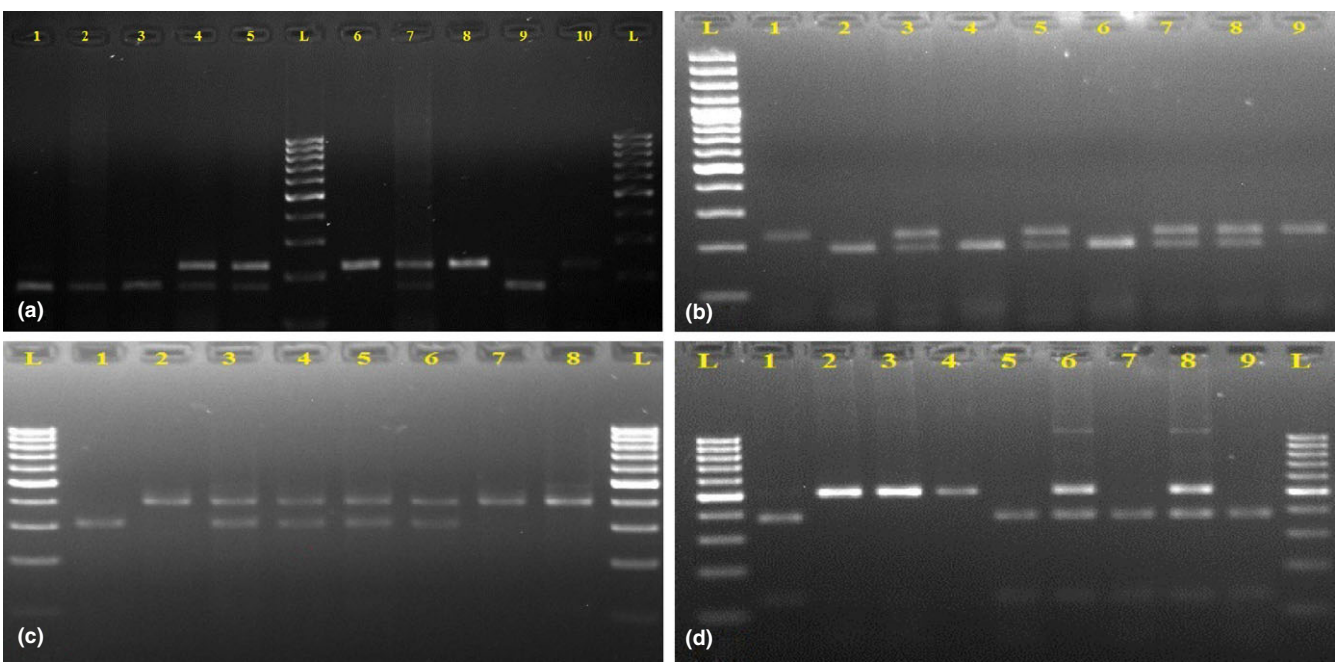


Figure 1 Agarose electrophorese pattern of GH (a), lanes 1–3 and 9: LL genotypes, lanes 4, 5 and 7: LV genotypes, lanes 6, 8 and 10: VV genotypes; STAT5A (b), lanes 1 and 9: TT genotypes; lanes 2, 4 and 6: CC genotypes; lanes 3, 5, 7 and 8: CT genotypes; LEP (c) lanes 2, 7 and 8: AA genotypes, lanes 3–6: AB genotypes, lane 1: BB genotype and MYF5 (d) lanes 2, 3 and 4: AA genotypes, lanes 6 and 8: AG genotypes, lanes 1, 5, 7 and 9: GG genotypes. L: DNA ladder (100 bp). [Colour figure can be viewed at wileyonlinelibrary.com]

Table 2; the least squares and standard errors for milk yield and quality traits of the genotypes belonging to *GH*, *STAT5A*, *LEP* and *MYF5* genes are provided in Table 3.

GH gene analysis

With regard to the *GH* gene of the Holstein Friesian cows used in this study, VV the genotype was not observed (Figure 1), the LL genotype was the most common genotype (86.2%) (Table 2), and there were significant relationships between *GH-Taq*I polymorphism and 305-day milk yield. The cows with the LL genotype had higher milk yields than the ones with the LV genotype ($P < 0.01$). However, no significant relationships were observed between *GH-Taq*I polymorphism and milk composition traits (Table 3).

STAT5A gene analysis

There were three genotypes (CC, CT and TT) identified in the *STAT5A* gene (Figure 1), and the CC genotype was the most common one (74.2%). There were no significant relationships between *STAT5A-Ava*I polymorphism and milk yield traits of Holstein Friesian cows (Table 3).

LEP gene analysis

There were three genotypes (AA, AB and BB) identified in the *LEP* gene of the Holstein Friesian cows (Figure 1): the AA genotype was the most common (55.1%), and the BB genotype was the least common (2.4%) (Table 2). *LEP-Sau3*AI polymorphism had significant relationships with the 305-day milk yield ($P < 0.01$), freezing point and lactose

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Table 2 *GH, STAT5A, LEP* and *MYF5* genotype and allele frequencies of Holstein Friesian cows.

Gene		*Genotype frequency*			*Allele frequency*		*Chi-square analysis (HWE)*
GH		LL	LV	VV	L	V	$\chi^2 = 0.91^{NS}$
	Observed	144 (86.2%)	23 (13.8%)	0	0.93	0.07	$P = 0.3401$ (df = 1)
	Expected	144.79	22.42	0.79			
STAT5A		CC	CT	TT	C	T	$\chi^2 = 0.01^{NS}$
	Observed	124 (74.2%)	40 (24%)	3 (1.8%)	0.86	0.14	$P = 0.9203$ (df = 1)
	Expected	124.17	39.66	3.17			
LEP		AA	AB	BB	A	B	$\chi^2 = 4.61^*$
	Observed	94 (55.1%)	69 (42.5%)	4 (2.4%)	0.77	0.23	$P = 0.0318$ (df = 1)
	Expected	97.93	59.14	8.93			
MYF5		AA	AG	GG	A	G	$\chi^2 = 11^{**}$
	Observed	17(10.2%)	102 (61.1%)	48 (28.7%)	0.41	0.59	$P = 0.0006$ (df = 1)
	Expected	27.69	80.62	58.69			

Significant at *0.05; **0.01.

Table 3 Least mean squares and standard error for milk yield and milk composition traits of the genotypes in *GH*, *STAT5A*, *LEP* and *MYF5* genes.

		Traits						
Gen		*Fat*	*Dry matter*	*Density*	*Protein*	*Freezing*	*Lactose*	*Milk yield (305 days)*
GH	LL	3.18 ± 0.08	9.10 ± 0.02	31.09 ± 0.15	3.44 ± 0.03	59.80 ± 0.16	4.99 ± 0.01	7638.7 ± 77.1^a
	LV	3.18 ± 0.10	9.05 ± 0.04	30.85 ± 0.24	3.39 ± 0.06	59.46 ± 0.26	4.97 ± 0.02	8988.3 ± 152.9^b
P								0.001
STAT5A	CC	3.21 ± 0.08	9.10 ± 0.02	31.08 ± 0.16	3.45 ± 0.03	59.86 ± 0.17	4.99 ± 0.01	7836.2 ± 83.8
	CT	3.10 ± 0.09	9.06 ± 0.03	31.01 ± 0.20	3.39 ± 0.04	59.48 ± 0.22	4.98 ± 0.02	7735.0 ± 125.6
	TT	3.21 ± 0.24	8.96 ± 0.09	30.55 ± 0.58	3.39 ± 0.15	59.05 ± 0.6	4.92 ± 0.05	7992.6 ± 417.4
P								
LEP	AA	3.14 ± 0.07	9.11 ± 0.03	31.15 ± 0.16	3.46 ± 0.03	59.96 ± 0.18^a	5.01 ± 0.01^a	7752.4 ± 94.9^a
	AB	3.23 ± 0.09	9.07 ± 0.03	30.99 ± 0.17	3.42 ± 0.04	59.57 ± 0.19^{ab}	4.97 ± 0.01^{ab}	7956.6 ± 98.3^a
	BB	3.14 ± 0.22	9.06 ± 0.09	30.25 ± 0.52	3.35 ± 0.13	58.95 ± 0.57^b	4.95 ± 0.05^b	6197.6 ± 373.8^b
P						0.0265	0.0211	0.001
MYF5	AA	3.29 ± 0.12	8.99 ± 0.05^a	31.29 ± 0.28	3.39 ± 0.07	59.56 ± 0.31	4.98 ± 0.02	7707.9 ± 188.5^a
	AG	3.19 ± 0.08	9.10 ± 0.03^b	30.98 ± 0.16	3.42 ± 0.03	59.77 ± 0.18	4.99 ± 0.01	7617.9 ± 89.1^a
	GG	3.13 ± 0.09	9.12 ± 0.03^b	31.12 ± 0.19	3.49 ± 0.04	59.79 ± 0.21	5.00 ± 0.02	8265.9 ± 116.1^b
P			0.0418					0.001

Means followed by the same letter in the same row do not differ by Tukey's test at 5% significance.

traits of the Holstein cows ($P < 0.05$) (Table 3). The cows with the BB genotype had worse milk yields than the other genotypes (Table 3).

MYF5 gene analysis

Three genotypes (AA, AG and GG) were identified in the *MYF5* gene of Holstein Friesian cows (Figure 1), and AG was the most common genotype (61.1%). *MYF5-Taq*I polymorphism had significant relationships with 305-day milk yield ($P < 0.01$) and dry matter content ($P < 0.01$) of the Holstein Friesian cows. The cows with GG genotype had higher milk yields than the other genotypes (Table 3).

DISCUSSION

*GH-Alu*I polymorphism

The VV genotype has not been identified in previous studies carried with different Holstein populations (Hradecká *et al.* 2008) or has been identified at only quite low frequencies in other studies (Khatami *et al.* 2005; Balogh *et al.* 2008). The VV genotype was also not identified in the Holstein Friesian

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cows of the present study. Such a case revealed that frequency of VV genotype might decrease due to selection favour of milk production traits in Holstein cows. However, though VV genotype not observed in our study, we hypothesized that VV genotype not totally vanish from the Holstein cattle population due to presence of heterozygous LV genotype.

Significant relationships were observed between *GH-Alu*I polymorphism and 305-day milk yield of the Holstein cows of this study, and the cows with the LV genotype had a higher milk yield than LL genotype (Table 3). Previous studies also have reported higher milk yields for LV-genotyped Holstein cows than the other genotypes (Balogh *et al.* 2008). Some other studies have reported higher milk yields for LL-genotyped cows than other genotypes only at the first lactation (Akyüz *et al.* 2015). There are also studies indicating non-insignificant relationships between *GH-Alu*I polymorphism and milk yield (Hradecká *et al.* 2008). Contrary to the present findings, significant relationships of *GH-Alu*I polymorphism with milk fat and protein have been reported (Khatami *et al.* 2005). With regard to the roles of growth hormone (*GH*) in milk production and udder development (Hradecká *et al.* 2008), *GH* is still considered a candidate gene for various yield traits. The present findings were considered to be promising outcomes for further studies to be carried out to improve milk yield traits of Holstein Friesian cows through *GH-Alu*I polymorphism. However, the present findings have also revealed that this polymorphism can not be used alone as a marker for milk yield traits.

*STAT5A-Ava*I polymorphism

In this study, 167 Holstein cows were found to be polymorphic with regard to *STAT5A-Ava*I polymorphism and the TT genotype was the least common genotype (Table 2). Similarly, the TT genotype has been reported to be the least common genotype in Holstein populations reared in Poland (Kmieć *et al.* 2010) and Iran (Sadeghi *et al.* 2009). On the other hand, the CC genotype was reported to be the least common genotypes in Holstein cows reared in Italy (Dario *et al.* 2009). Such different observations may be related to number of animals investigated in those studies.

Since it is located on the somatic axis, the relationships of *STAT5A-Ava*I polymorphism with milk yield traits were also investigated in this study and the relationships of this polymorphism with milk yield traits of Holstein cows were not found to be significant. However, in a study carried out in Iran, TC-genotyped cows had higher milk protein values than the other genotypes (Sadeghi *et al.* 2009). On the other hand, there are other studies reporting significant relationships between different SNPs of *STAT5A* gene and lactation milk yield traits of Holstein cows (Flisikowski *et al.* 2004; Oikonomou *et al.* 2011; He *et al.* 2012). With regard to *STAT5A-Ava*I polymorphism, CC-genotyped Simmental cows had higher milk and protein yields than the other genotypes at the 3rd lactation (Cosier *et al.* 2010). Similarly, with regard to the *STAT5A-Ava*I polymorphism, CC-genotyped Jersey cows had higher milk, fat-free dry matter, fat and protein yields than the other genotypes (Dario and Selvaggi 2011). Such cases revealed that the relationships between *STAT5A-Ava*I genotypes and yield traits might vary with in the cattle breeds. Therefore, there is a need for further studies investigating greater number of breeds and animals.

*LEP-Sau3*AI polymorphism

The leptin hormone, related to energy balance and appetite, is a significant hormone in mammals (Zieba *et al.* 2008). Therefore, the gene encoding the leptin hormone may be useful in improving important yield traits. Couple SNPs in *LEP* gene were reported to have relationships with significant yield traits (Lagonigro *et al.* 2003). Therefore, *Sau3A*I polymorphism was investigated in this study. The Holstein Friesian cows investigated here were found to be polymorphic with regard to *LEP-Sau3A*I polymorphism: the AA genotype was the most common, and the BB genotype was the least common genotype. These findings comply with the results of earlier studies carried out with Holstein cows in Iran (Sharifzadeh and Doosti 2010), Greece (Oikonomou *et al.* 2009), Jordan (Jawasreh *et al.* 2009) and Turkey (Özdemir 2011). Such cases were mostly because of lower milk yield trait values of BB-genotyped cows than the others. In the present study, BB-genotyped cows had the owest milk yield during the 305-day lactation and despite non-significant differences, the AB-genotyped cows were better than AA-genotyped cows (305-day milk yields, respectively, as 7956.6 and 7752.4) (Table 3). Similarly, AB-genotyped Holstein Friesian cows in Iran had higher milk yields than the other genotypes (Javanmard *et al.* 2010). Significant relations of other SNPs of *LEP* gene of Holstein cows with milk yield and milk composition have also been reported in previous studies, and thus these SNPs have been reported as being used in improving milk yield traits (Oikonomou *et al.* 2011). On the hand, there are other studies reporting non-insignificant relationships of SNPs in *LEP* gene with milk yield traits (Komisarek *et al.* 2005). It was concluded, based on the present and earlier findings, that the *LEP* gene was a promising gene to be used in improving milk yield traits during a 305-day lactation period.

*MYF5-Taq*I polymorphism

In a previous study carried out with Holstein cows in Turkey, AA was reported as the least (0.7%) and AG was reported as the most (50%) common genotype (Şahin and Akyüz 2017). Similarly, in the 167 Holstein cows of the present study, AA was the least (10.2%) and AG was the most (61.1%) common genotype. Previous researchers have investigated the relationship of the polymorphisms in *MYF5* gene with growth parameters (Seong *et al.* 2011) and meat quality (Wei *et al.* 2011) of farm animals. There were no studies in the literature investigating relationships between

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*MYF5-Taq*I polymorphism and milk yield traits. In the present study, GG-genotyped cows had significantly better milk yields than the other genotypes during the 305-day lactation period. With regard to fat-free dry matter, the AA-genotyped cows were worse than the other genotypes. The present findings show that *MYF5-Taq*I polymorphism could be used as a marker for milk yield traits of dairy cows.

CONCLUSIONS

Based on the findings of this study, it was concluded that *GH-Taq*I, *LEP-Sau3A*I and *MYF5-Taq*I polymorphisms of the genes investigated had significant effects, especially on the 305-day milk yield of Holstein cows, and thus they could be used as candidate genes in marker-assisted selection studies to improve this trait. Previously reported effects of *MYF5-Taq*I polymorphism on growth parameters and meat quality were, for the first time, indicated for milk yield traits in this study. However, further studies should be carried out with a greater number of breed and animals to better elucidate the relationships of these SNPs with milk yield and milk composition.

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