Quantitative Trait Loci Affecting Milk Production Traits on BTA 14 in Iranian Holstein Dairy Cattle: A Confirmation

Research Article

M. Noorisadegh[1], S. Ansari-Mahyari[2*], M.P. Eskandai Nasab[1] and F. Rafeie[3]

[1] Department of Animal Science, College of Agriculture, University of Zanjan, Iran
[2] Department of Animal Science, College of Agriculture, Isfahan University of Technology, Isfahan, Iran
[3] Department of Agricultural Biotechnology, Faculty of Agricultural Science, University of Guilan, Rasht, Iran

*Correspondence E-mail: s.ansari@cc.iut.ac.ir

ABSTRACT

The aim of this study was to refine the position of previously detected quantitative trait loci (QTL) on bovine chromosome 14 affecting milk production traits, using both linkage analysis (LA) and combined disequilibrium and linkage analysis (LDLA) methods, in Iranian Holstein dairy cattle. Analysis data was LRT (likelihood ratio test) and computed using the DMU (estimate the (co)variance components based on the average information of restricted maximum likelihood) and the results were compared with chi-square test and finally, the most likely location of QTLs was identified (P<0.05). A daughter design with 232 daughters from 10 sire families were considered and 10 microsatellite markers with a map distance of 0 to 63 cM located between markers ILSTS039 and DIK4361 (ILSTS011, DIK2598, DIK4884, DIK5080, CBDIKM002, ILSTS039, BM1508, CSSM066, CBDIKM004, and DIK4361) were genotyped. For milk and fat yield traits, the two mapping methods revealed a highly significant QTL was located within 20 to 60 and 54 to 60 cM interval (using LA) and within 12 to 60 and 60 cM interval (using LDLA), respectively. For fat percentage, a highly significant QTL was detected within 3, 12, 20, 36, 44 and 50 cM (using LA), but for LDLA, no significant location was detected. These results confirmed the findings of suggestive QTLs affecting milk production traits in the previous studies. Besides, the identified QTL in this study could be considered for marker-assisted evaluation and also for the selection of a refined set of candidate genes affecting the economic traits in Iranian dairy cattle breeding schemes.

KEY WORDS Iranian Holstein cows, LA, LDLA, milk production, QTL.

INTRODUCTION

The most important economic traits such as milk production and disease resistance have a continuous underlying distribution of measurement and the genes responsible for genetic variation in these traits have been termed quantitative trait loci (QTL) (Georges *et al.* 1995). A major objective of the QTL studies in livestock breeding schemes is to detect the markers that can be implemented in breeding programs via marker-assisted selection (MAS). Milk production is one of the economically important sectors in dairy cattle industries. In Iran, milk consumption per capita is about half the world average (85-90 liter). Iranian dairy production has undergone significant and considerable structural changes during the last two decades due to creating larger herds. In 1966, total cattle population of Iran was 4.9 million but it has reached 7.9 million cattle (mainly Holstein) in the last three decades (Ebrahimi-Hoseinzadeh *et al.* 2015a). In 2017 year, cattle population of Iran 1 million mainly and 5/4 million blended reported (Association

of animal feed and aquatic animals, http://t.me/irfia_channel). The QTL mapping has mainly focused on milk production traits. Simulation studies have shown that MAS has a significant effect on the genetic progress of these traits (Kashi *et al*. 1990; Meuwissen and Goddard, 1996). Many other important QTLs have been reported by linkage information since the first QTL experiment on milk production was reported by Georges *et al*. (1995).

Even though QTLs for milk production traits have been found in almost every bovine autosome chromosomes, but BTA14 is one of the most concerned chromosomes in QTL mapping linked with the milk production traits such as milk yield, fat percentage, fat content, fat yield, protein percentage and protein yield (Arranz *et al*. 1998; Ashwell *et al*. 1998; Khatkar *et al*. 2004).

In early 2003-2018, via genome scan based on marker-QTL linkage analysis and reported 9239 QTLs were located on chromosome 14 (http://www.animalgenome.org/cgi-bin/QTLdb/index).

It has also been shown that BTA14 region was found to harbor of diacylglycerol acyltransferase 1 (*DGAT1*) and cytochrome P450, family 11, subfamily B member 1 (*CYP11B1*) genes (Kaupe *et al*. 2007). *DGAT1* is a microsomal enzyme that catalyzes the synthesis of triglycerides from diglycerides and acyl-coenzyme A (Cases *et al*. 1998; Furbass *et al*. 2006).

Considering the role of *DGAT1* in lipid metabolism and also QTL studies for milk production traits, *DGAT1* has been regarded as a good positional candidate gene affecting milk production traits in dairy cattle (Grisart *et al*. 2002; Furbass *et al*. 2006).

CYP11B1 encodes an enzyme called 11-beta-hydroxylase that is found in the adrenal glands and is positively associated with fat content (Kawamoto *et al*. 1990; Curnow *et al*. 1991). In Iranian Holstein dairy cattle compared to other countries, applying different breeding goals and selection criteria over generations may have resulted in differences in the genetic background of cattle compared to other populations.

Although many studies have been conducted on Iranian cattle QTLs affecting milk yield, fat yield and fat percentage of these cattle have not been studied yet using random regression models (Alinaghizadeh *et al*. 2007; Javanmard *et al*. 2008; Mohammadi *et al*. 2009; Mohammad-Abadi *et al*. 2010; Kharrati-Koopaei *et al*. 2012a; Kharrati-Koopaei *et al*. 2012b; Pasandideh *et al*. 2015; Barazandeh *et al*. 2016). Hence, the main purpose of this study was to confirm the suggestive location and maps of the possible QTLs affecting milk yield, fat yield and fat percentage on chromosome 14 in Iranian Holstein dairy cattle using linkage (LA) and linkage disequilibrium (LDLA) information.

MATERIALS AND METHODS

Population and phenotypic data

In the current study, all the cows were in similar intensive dairy farms. The daughters were randomly selected from 10 sire family groups of Iranian Holstein dairy cattle across 58 herds located in the different regions of Iran (Tehran, Isfahan, Markazi, Khorasan, Zanjan, Fars, Yazd and Qazvin).

Family sizes varied between 9 to 41 dairy cows with 24 daughters on the average. Semen samples of all sires were obtained from National Animal Breeding Center of Iran and blood samples were collected from 233 cows based on a daughter design approach (Table 1). Phenotypic data were collected for milk yield (MY), fat yield (FY) and fat percentage (FP). All phenotypic data were collected based on twice daily milking by National Animal Breeding Center and Promotion of Animal Products of Iran in 2009-2010.

DNA extraction and genotyping

Genomic DNA was purified from semen sires by using salting out method (Weyrich, 2012) and blood samples by using AccuPrep® Genomic DNA Extraction Kit (Bioneer, Korea), respectively. For genotyping 10 sires and their daughters, on chromosome 14 with a distance 0 to 63 cM, ten microsatellite markers (ILSTS011 (blue,6-FAM^{TM}), DIK2598 (blue,6-FAM^{TM}), DIK4884 (yellow,NED^{TM}), DIK5080 (green,VIC), CBDIKM002 (blue,6-FAM^{TM}), ILSTS039 (blue,6-FAM^{TM}), BM1508 (green,VIC), DIK4361 (yellow,NED^{TM}), CBDIKM004 (yellow,NED^{TM}) and CSSM066 (green,VIC) respectively label color and fluorescent lable) were used (Table 2). The average distance between markers in the linkage groups was 6.5 cM. PCR amplifications were performed in 15 μL reactions each containing 1.5 ng genomic DNA, 2.5 m*M* MgCl$_2$ (Fermentas, USA), 0.2 m*M* dNTPs mix (Roche Applied Science, Germany), 10 pmol each primer (Metabion, Germany), 1X PCR buffer (Fermentas, USA) and 0.5 U Taq DNA polymerase (Fermentas, USA). Amplifications were performed using the Gene Amp PCR 9700 (Applied Biosystems, USA). The PCR conditions were as follows: an initial denaturation for 5 min at 95 ˚C, followed by 30 cycles of 30 sec at 95 ˚C, 45 sec at 59 ˚C or 60 ˚C, 30 sec at 72 ˚C and a final extension of 10 min at 72 ˚C. Genotyping was performed using Applied Biosystems 3130 Genetic Analyzer. Allele sizes were determined using Gene Mapper v.4.0 (Applied Biosystems, USA).

Statistical analysis

Milk production records were analyzed using a mixed model in which QTL was considered as a random effect. The variance components of QTL effects were estimated to examine the putative QTL positions.

Table 1 Distribution of the informative samples of 10 half-sib sires families

Family	1	2	3	4	5	6	7	8	9	10	Total
Informative	33	24	41	29	13	33	22	14	9	15	233

Table 2 Details of the ten microsatellite markers used in current study

Microsatellite markers	Position (cM)	Primer (5'→3') (color label)	Numbers of daughters	Alleles	Reference
ILSTS011	25	F:CCTAATGACTACCAACAGGG (blue) R:TCCATGGAATCACAAAGAGC	218	6	Brezinskyel *et al.* (1993)
DIK2598	51	F:GCCCATGGCAGTGTTATTTA (blue) R:CAAGTCCATCCAAATTGCT	232	12	Ihara *et al.* (2004)
DIK4884	56	F:TCAAAAATGGCTCTATGTACGTG (yello) R:GTCAGTCGTTGGGTCTTGGT	220	7	Ihara *et al.* (2004)
DIK5080	31	F:GGATCAGGTCTGCAGATTCC (green) R:CCTTTGGCTGAGAAGTCTGG	219	11	Ihara *et al.* (2004)
CBDIKM002	41	F:GTGAAAAGAGGATTAGCAGC (blue) R:GAGCAACTGAACAACAAACC	230	7	Ihara *et al.* (2004)
ILSTS039	0	F:CCTAATGACTACCAACAGGG (blue) R:TCCATGGAATCACAAAGAGC	232	7	Kemp *et al.* (1995)
BM1508	17	F:CAGGTGTACAGCAAACTGAATC (green) R:CGTCAAAACATTCGTTCAG	216	4	Alexander *et al.* (1995)
DIK4361	63	F:GTTAATGGCGAGCCCCTCA (yello) R:GCCCGTTTATCACCATCAAG	206	5	Ihara *et al.* (2004)
CBDIKM004	47	F:GTGAAAAGAGGATTAGCAGC (yello) R:GAGCAACTGAACAACAAACC	224	9	Ihara *et al.* (2004)
CSSM066	5	F:ACACAAATCCTTTCTGCCAGCTGA (green) R:AATTTAATGCACTGAGGAGCTTGG	217	10	Maddox *et al.* (2001)

Gametic relationship matrix for QTL alleles of any two founder haplotypes was computed based on two methods: linkage analysis (LA) within sire groups (Wang *et al.* 1995) and joint analysis across sire groups using linkage (LA) and linkage disequilibrium (LDLA) information (Meuwissen and Goddard, 2001).

The following equation was used as a generalized linear model:

$$y = Xb + Za + Wg + e$$

Where:

y: vector of observations (records of the traits).
b: vector of fixed effects (herd-year-season).
a: vector of random animal effects.
g: vector of random QTL effects.
e: vector of random residual effects.
X, Z, W: design matrix which related records to fixed, random animal and random QTL effects, respectively.

It was assumed that the genetic effects (a), QTL effects (g) and residual effects (e) were normally distributed as $a \sim N(0, A\sigma^2_a)$, $g \sim N(0, HP\sigma^2_g)$ and $e \sim N(0, I\sigma^2_e)$, respectively:

Where:

A: additive relationship matrix.

HP: identical by descent (IBD) matrix that contains the IBD probabilities for the QTL at location p.
I: an identity matrix.

The IBD probabilities for the QTLs based on the haplotypes were calculated using the analytical method suggested by Meuwissen and Goddard (2001). The DMU package (Madsen and Jensen, 2002) was used to estimate the (co)variance components based on the average information of restricted maximum likelihood. This algorithm approached the restricted likelihood to maximize with respect to variance components associated with the random effects (Sorensen *et al.* 2003). The parameters were estimated at the marker brackets along the chromosome region. Hypothesis tests to detect QTLs were performed with the likelihood ratio test (LRT) as follows:

$$LRT = -2 \times [\text{log likelihood}_{(reduced)} - \text{log likelihood}_{(full)}]$$

Where:

log likelihood$_{(reduced)}$: log likelihood of a model excluding the QTL effects (no QTL model).
log likelihood $_{(full)}$: log likelihood of a model with a QTL effects.

It was assumed that LRT was a statistic with chi-squared distribution and degree of freedom (DF)= 1.

According to 10 markers used in this study and with respect to possibility to calculate probability of inheritance of favorable allele of QTL in each location between two markers, 9 locations were assumed to be located between two markers. Then, LRT was computed using the DMU (Madsen and Jensen, 2002) and the results were compared with chi-square test and finally, the most likely location of QTLs was identified (P<0.05).

RESULTS AND DISCUSSION

Different family sizes in Table 1 indicated that factors such as the number of samples with genotypes and imbalance of allele segregation in markers could be more effective and informative (Esmailizadeh *et al*. 2006). The information content of the individuals is the proportion of animals in which the allele inherited from the sire can be unambiguously identified (Table 2).

Three traits were evaluated to refine and confirm the detected QTL affecting milk yield and composition. This study successfully confirmed the mapped QTL for MY, FY and FP in Iranian Holstein dairy cattle. The genomic relationship information for mapping of the reported QTLs was based on both LA and LDLA approaches. QTL mapping using LD information across half-sib families and using LDLA can decrease the required number of phenotyped and genotyped individuals, compared to LA method (Ansari-Mahyari *et al*. 2009). Also, compared with LA, LDLA utilizes all historical genomic information in gametic relationship matrix between founders using linkage disequilibrium information and would be more informative for the inference (Hu *et al*. 2010). This method has been used widely in dairy cattle genomic studies.

The significant QTLs in the most probable location (P<0.05) are shown in Table 3. Although the results from LA method indicated several QTLs for fat percentage (FP) could be located at 3 to 20 and 36 to 50 cM, the most likely location was at 3 cM (P<0.05). In addition, for fat yield (FY) a location was significant at 20 to 60 cM, while the most likely position was at 54 cM (P<0.05). For milk yield (MY), significant location was at 54 to 60 cM but the most likely position was revealed to be at 54 cM (P<0.05) (Figures 1 and 3). Using microsatellite markers in dairy cattle, many studies have found that segregated QTLs for milk production traits in several autosome bovine chromosomes (Khatkar *et al*. 2004).

For example in different Holstein dairy cattle, several studies have reported the segregation of at least one QTL in the middle of BTA6, affecting one or more of the milk production traits, close to marker BM143 (Kühn *et al*. 1999; Velmala *et al*. 1999; Nadesalingam *et al*. 2001; Ron *et al*. 2001).

To date, various QTLs affecting milk production traits have been identified on BTA14 in Holstein dairy cows. A major QTL affecting milk yield and composition on the centromeric end of BTA14 (DGAT1 K232A mutation) was first reported by Coppieters *et al*. (1998). The QTL mapping studies on BTA14 has showed that the markers were linked to the genes controlling important production traits. Other studies suggested that ILSTS039, CSSM066 and BM1508 markers were nearest markers to the fat percentage QTL (Heyen *et al*. 1999; Biochard *et al*. 2003; Ashwell *et al*. 2004).

Most of the identified QTL regions for milk production traits in the current study have been previously reported in the other literature. Recently, Aliloo *et al*. (2015) confirmed genome regions with validated additive effects on milk yield on *Bos taurus* autosome 14 in Holstein and Jersey cows. Iso-Touru *et al*. (2016) reported that *Bos taurus* BTA14 is significantly (P<0.05) associated with fat yield in the DGAT1 gene, (region: from 1448510 bp to 2271832 bp) and milk yield (region: from 1448510 bp to 2271832 bp) in Nordic Red cattle using imputed whole genome sequence variants.

They claimed that the strongest association with milk and fat yield was found on BTA14. Also, the chromosome 14 polymorphisms have been scanned for milk production traits in commercial half-sib families of French dairy goats. Martin *et al*. (2017) found 5 polymorphisms (positions: 0.033, 0.037, 0.111, 0.123 and 0.155 MB) that are significantly related to fat content and fat yield, base Illumina Goat SNP 50 Bead Chip.

The results from the current study confirmed precisely those QTLs obtained by others in Iranian Holstein dairy cows. Besides, the QTL obtained by LDLA method showed that for milk yield a detection was observed at 12 to 20 and 60 cM, but significant positions were at 12 and 60 cM (P<0.05). Although, the most likely position affecting fat yield was detected at 60 cM on chromosome 14 (P<0.05) (Figures 2 and 3). Therefore, it could be concluded that current results on QTL mapping for milk and fat yield traits using LDLA information confirmed the result reported by Bennewitz *et al*. (2004) (marker:DGAT1). In addition, the results for milk yield QTL locations were in accordance with Bagnato *et al*. (2008) (marker:BMS1748) and Schnabel *et al*. (2005) (marker:BMS1899).

Estimation of QTL, polygenic and residual variance components in 9 significant locations between each of the two markers (Table 4) indicated that QTL and polygenic variances for the most likely locations were greater than their residual variances. When applying LDLA, all variance components (genetic and non-genetic) were close to the true values and the estimates indicated lower standard error than LA (Ansari-Mahyari *et al*. 2009).

Table 3 Most probable locations (P<0.05) for MY, FY and FP on chromosome 14 using linkage analysis (LA) and linkage disequilibrium (LDLA) methods

Trait	Location (cM)	Analysis method	Like lihood ratio test	Marker bracket
Fat %	3	LA	5.1	ILSTS039-CSSM066
Fat yield	54	LA	5.4	DIK2598-DIK4884
Milk yield	54	LA	12.2	DIK2598-DIK4884
Fat yield	60	LDLA	5.5	Dik4884-Dik4361
Milk yield	12.60	LDLA	7.5	CSSM066-BM1508
Milk yield	60	LDLA	4	Dik4884-Dik4361
Fat %	-	LDLA	-	No significant location was detected
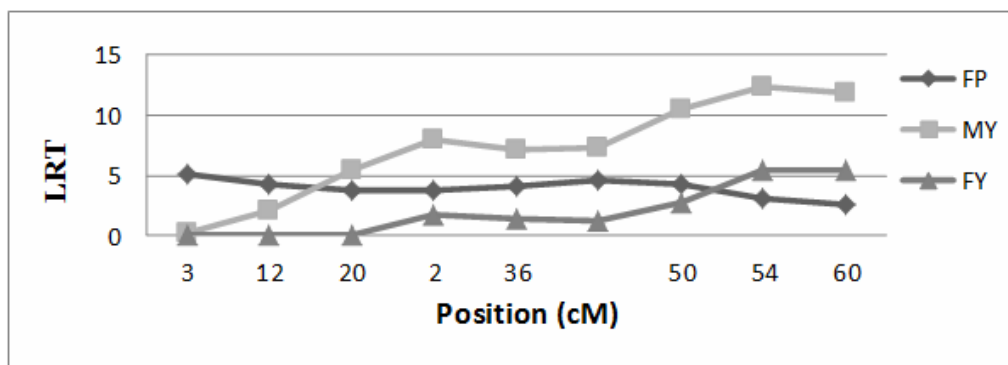
Figure 1 Significant and likely positions of the QTL for MY, FY, and FP using LA method (MY: milk yield; FP: fat percentage; FY: fat yield; LRT: likelihood ratio test and LA: linkage analysis)
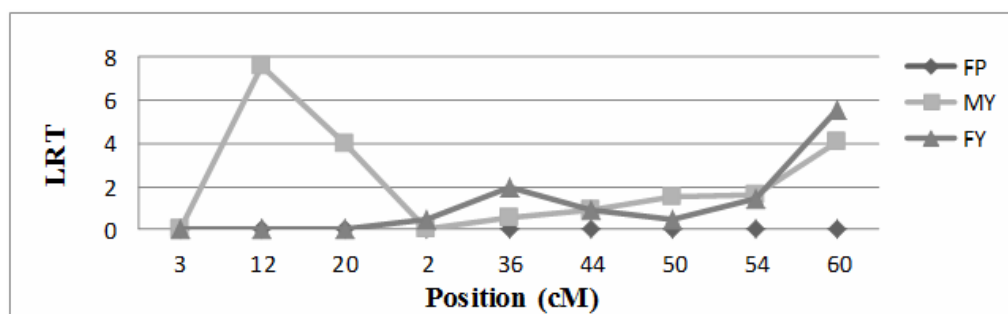
Figure 2 Significant and likely positions of the QTL for MY, FY, and FP using LDLA method (MY: milk yield; FP: fat percentage; FY: fat yield; LRT: likelihood ratio test and LDLA: linkage disequilibrium)
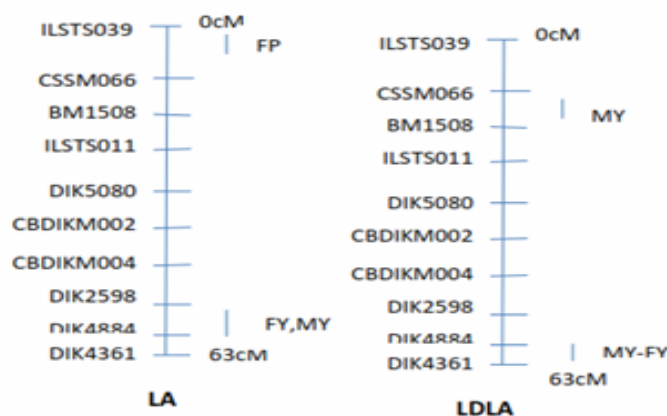
Figure 3 Likely positions estimated for milk yield and milk compositions traits mapped chromosome 14using LA and LDLA methods (MY: milk yield; FP: fat percentage; FY: fat yield; LA: linkage analysis and LDLA: linkage disequilibrium)

Table 4 Estimated variance components of the most likely locations and percentages of phenotypic variance of MY, FY and FP on chromosome 14 using linkage analysis (LA) and linkage disequilibrium (LDLA) methods

Analysis methods	Traits	QTL variance	Polygenic variance	Residual variance	Phenotypic variance	Trait percentage
LA	Fat yield	334.5519	803.2505	460.4909	289.3642	0.1761
	Milk yield	391041.9	802967.6	379951.2	235165	0.2257
	Fat percentage	0.0248	0.0562	0.0235	1.433	67.004
LDLA	Fat yield	235.1623	536.0951	412.4783	130.81	3.399
	Milk yield	186907.8	373932.7	290673.7	1202433.5	3.6615
	Fat percentage	0.0133	0.0171	0.0229	-	-

Based on LA method, the estimated QTL variance were 3877209 to 43575.5, 47.92 to 38.68, and 3.34 to 2.29 for MY, FY and FP, respectively. Based on the LDLA information, the estimated QTL FP respectively. Estimation of polygenic variance were 81331.1 to 88921.3, 108.007 to 88.65 and 6.8 to 5.8 for MY, FY, and FP, respectively. The polygenic variance for MY, FY and FP were 81331.1 to 88921.3, 108.007 to 88.65 and 6.8 to 5.8 respectively based on LA method, and 38044 to 41889.4, 52.67 to 61.07 and 1.92 to 1.77 respectively based on LDLA information. Residual variance size for MY, FY and FP ranged from 40901.3 to 39840.3, 56.86 to 48.41, and 2.58 to 2.50, respectively based on LA and 31754 to 32175, 45.41 to 46.63 and 2.55 to 2.52, for LDLA method. In Table 4, estimated variance components of the most likely locations for MY, FY and FP in two methods are shown. The results indicated that a greater proportion of the total variance can be explained by the effects, as also reported by Szyda *et al*. (2005).

However, MY and FP had the largest trait percentages (ratio of QTL variance to phenotypic variance; Table 4), which can improve the power of QTL detection in QTL fine-mapping. The power of this analysis ranged from 0.15 to 0.35. The proportional QTL variance showed the contribution of specific trait loci to the total phenotypic variance of the trait.

In each position mapping QTL using the desirable model determines whether a significant amount of the variance in a quantitative trait can be associated with the QTL in proposed position. QTL variance determined as the reduction of the residual variance acquired by fitting the QTL in the location was relatively small for the detection (Sohrabi *et al*. 2012).

In the current study, according to variance component estimated in LA method, the largest ratio of polygenic and residual variances to phenotypic variance, QTL variance to residual variance and QTL variance to polygenic variance was observed for FP position at 60 cM, 50 cM and 60 cM, respectively. Also, in LDLA method, the largest ratio of polygenic variance to residual variance, QTL variance to residual variance and QTL variance to residual variance

estimated for FP was refined at 54 cM, 54 cM and 60 cM, respectively.

CONCLUSION

In conclusion, the two methods considered in this study (LA and LDLA) showed a highly significant QTL located within 20 to 60 and 54 to 60 cM interval and within 12 to 60 and 60 cM interval for milk and fat yield traits, respectively. Also, a highly significant QTL for fat percentage was detected at 3, 12, 20, 36, 44 and 50 cM with LA method. The results suggest a possible use of these candidate markers in gene-assisted selection programs for improvement of milk production traits in Iranian dairy cattle, although large-scale studies in different breeds are required.

ACKNOWLEDGEMENT

REFERENCES

Alexander L.J., Rohrer G.A., Stone R.T. and Beattie C.W. (1995). Porcine SINE-associated microsatellite markers: Evidence for new artiodactyl SINEs. *Mamm. Genome.* **6(7),** 464-468.

Aliloo H., Pryce J.E., González-Recio O., Cocks B.G. and Hayes B.J. (2015). Validation of markers with non-additive effects on milk yield and fertility in Holstein and Jersey cows. *BMC Genet.* **16,** 89-97.

Alinaghizadeh R., Mohammad-Abadi M.R. and Moradnasab-Badrabadi S. (2007). Kappa-Casein gene study in Iranian Sistani cattle breed (*Bos indicus*) using PCR-RFLP. *Pakistan J. Biologi. Sci.* **10(23),** 4291-4294.

Ansari-Mahyari S., Berg P. and Lund M.S. (2009). Fine mapping quantitative trait loci under selective phenotyping strategies based on linkage and linkage disequilibrium criteria. *J. Anim. Breed. Genet.* **126,** 443-454.

Arranz J.J., Coppieters W., Berzi P.N., Cambisano B., Grisart L., Karim F., Marcq L., Moreau C., Mezer J., Riquet P., Simon P., Vanmanshoven D., Wagenaar A. and Georges M. (1998). A QTL affecting milk yield and composition maps to bovine

chromosome 20: a confirmation. *Anim. Genet.* **29,** 107-115.

Ashwell M.S., Da Y., Van Raden P.M., Rexroad C., Jr E. and Miller R.H. (1998). Detection of potential loci affecting conformation type traits in an elite US Holstein population using microsatellite markers. *J. Dairy Sci.* **81,** 1120-1125.

Ashwell M.S., Heyen D.W., Sonstegard T.S., Van-Tassell C.P., Da Y.P., Van-Raden M., Weller M. and Lewin H.A. (2004). Detection of quantitative trait loci affecting milk production, health, and reproductive traits in Holstein cattle. *J. Dairy Sci.* **87,** 468-475.

Bagnato A., Schiavini F., Rossoni A., Maltecca C., Dolezal M., Medugorac I., Solkner J., Russo V., Fontanesi L., Friedmann A., Soller M. and Lipkin E. (2008). Quantitative trait loci affecting milk yield and protein percentage in a three-country Brown Swiss population. *J. Dairy Sci.* **91,** 767-783.

Barazandeh A., Mohammad-Abadi M.R., Ghaderi M. and Nezamabadipour H. (2016). Predicting CpG Islands and their relation ship with genomic feature in cattle by hidden markov model algorithm. *Iranian J. Appl. Anim. Sci.* **6(3),** 571-579.

Bennewitz J., Reinsch N., Paul S., Looft C., Kaupe B., Weimann C., Erhardt G., Thaller G., Kuhn C., Schwerin M., Thomsen H., Reinhardt F., Reents R. and Kalm E. (2004). The DGAT1 K232A mutation is not solely responsible for the milk production quantitative trait locus on the bovine chromosome 14. *J. Dairy Sci.* **87,** 431-442.

Biochard D., Grohs C., Bourgeois F., Cerqueira F., Faugeras R., Neau A., Rupp R., Amigues Y.Y., vonne-Boscher M. and Leveziel H. (2003). Detection of genes influencing economic traits in three French dairy cattle breeds. *Genet. Sel. Evol.* **35,** 77-101.

Brezinsky L., Kemp S.J. and Teale A.J. (1993). Five polymorphic bovine microsatellites (ILSTS010-014). *Anim Genet.* **24(1),** 75-76.

Cases S., Smith S.J., Zheng Y.W., Myers H.M., Lear S.R., Sande E., Novak S., Collins C., Welch C.B., Lusis A.J., Erickson S.K. and Farese R.V.J. (1998). Identification of a gene encoding an acyl CoA: Diacylglycerol acyltransferase, a key enzyme in triacylglycerol synthesis. *Proc. Natl. Acad. Sci.* **95(22),** 13018-13023.

Coppieters W.J., Riquet J.J., Arranz P., Berzi N., Cambisano B., Grisart L., Karim F., Marcq L., Moreau C., Nezer P., Simon P., Vanmanshoven D. and Wagenaar D. (1998). A QTL with major effect on milk yield and composition maps to bovine Chromosome 14. *Mamm. Genome.* **9,** 540-544.

Curnow K.M., Tusie-Luna M.T. and Pascoe L. (1991). The product of the CYP11B2 gene is required for aldosterone biosynthesis in the human adrenal cortex. *Mol. Endocrinol.* **5,** 1513-1522.

Ebrahimi-Hoseinzadeh Z., Mohammad-Abadi M.R., Esmailizadeh A.K., Khezri A. and Najmi-Noori A. (2015a). Association of PIT1 gene with milk fat percentage in Holstein cattle. *Iranian J. Appl. Anim. Sci.* **5(3),** 575-582.

Esmailizadeh A.K., Pitchford W.S., Bottema C.D.K., Verbyla A.P. and Gilmour A.R. (2006). Mapping multiple QTL for birth weight in cattle growth using a mixed model approach. Pp. 17-20 in Proc. 8th World Congr. Genet. Appl. Livest. Prod., Belo Horizonte, Brazil.

Furbass R., Winter A., Fries F. and Kuhn C. (2006). Alleles of the bovine DGAT1 variable number of tandem repeat associated with a milk fat QTL at chromosome 14 can stimulate gene expression. *Physiol. Genomics.* **25,** 116-120.

Georges M., Nielsen D., Mackinnon M., Mishra A., Okimoto R., Pasquino A., Sargeant T.L.S.A., Sorensen M., Steele R. and Zhao X. (1995). Mapping quantitative trait loci controlling milk production in dairy cattle by exploiting progeny testing. *Genetics.* **139,** 907-920.

Grisart B., Coppieters W., Farnir F., Karim L., Ford C., Berzi P., Cambisano N., Mni M., Reid S., Simon P., Spelman R., Georges M. and Snell R. (2002). Positional candidate cloning of a QTL in dairy cattle: identification of a missense mutation in the bovine *DGAT1* gene with major effect on milk yield and composition. *Genome Res.* **12,** 222-231.

Heyen D.W., Weller J.I., Ron M., Band M., Beever J.E., Feldmesser E., Da Y., Wiggan G.R., Vanraden P.M. and Lewin H.A. (1999). A genome scan for QTL influencing milk production and health traits in dairy cattle. *J. Physiol. Genome.* **1,** 165-175.

Hu F., Liu J., FZ B., Zeng X., Ding D., Yin C., Gong C. and Zhang Y.Z. (2010). QTL identification using combined linkage and linkage disequilibrium mapping for milk production traits on BTA6 in Chinese Holstein population. *Asian-Australasian J. Anim. Sci.* **23,** 1261-1267.

Ihara N., Takasuga A., Mizoshita K., Takada H., Sugimoto M., Mizoguchi Y., Hirano T., Itoh T., Watanabe T., Reed K.M., Snelling W.M., Kappes S.M., Beattie C.W., Bennett G.L. and Sugimoto Y. (2004). A comprehensive genetic map of the cattle genome based on 3802 microsatellites. *Genome Res.* **14,** 1987-1998

Iso-Touru T., Sahana G., Guldbrandtsen B., Lund M.S. and Vilkki J. (2016). Genome-wide association analysis of milk yield traits in Nordic Red cattle using imputed whole genome sequence variants. *BMC Genet.* **17,** 55.

Javanmard A., Mohammad-Abadi M.R., Zarrigabayi G.E., Gharahedaghi A.A., Nassiry M.R., Javadmansh A. and Asadzadeh N. (2008). Polymorphism within the intron region of the bovine leptin gene in Iranian Sarabi cattle (Iranian *Bos taurus*). *Russian J. Genet.* **44(4),** 495-497.

Kashi Y.E., Hallerman E. and Soller M. (1990). Marker-assisted selection of candidate bulls for progeny testing programmes. *Anim. Prod.* **51,** 63-74.

Kaupe B., Brandt H., Prinzenberg E.M. and Erhardt G. (2007). Joint analysis of the influence of *CYP11B1* and *DGAT1* genetic variation on milk production, somatic cell score, conformation, reproduction, and productive lifespan in German Holstein cattle. *J. Anim. Sci.* **85,** 11-21.

Kawamoto T., Mitsuuchi Y. and Ohnishi T. (1990). Cloning and expression of a cDNA for human cytochrome P-450 aldo as related to primary aldosteronism. *Biochem. Biophys. Res. Commun.* **173,** 309-316.

Kemp S.J., Hishida O., Wambugu J., Rink A., Longeri M.L., Ma R.Z., Da Y., Lewin H.A., Barendse W. and Teale A.J. (1995). A panel of polymorphic bovine, ovine and caprine microsatellite markers. *Anim. Genet.* **26(5),** 299-306.

Kharrati-Koopaei H., Mohammad-Abadi M.R., Ansari-Mahyari

S., Tarang A.R., Potki P. and Esmailizadeh A.K. (2012a). Effect of DGAT1 variants on milk composition traits in Iranian Holstein cattle population. *Anim. Sci. Pap. Rep.* **30(3),** 231-240.

Kharrati-Koopaei H., Mohammad-Abadi M.R., Tarang A. and Esmailizadeh A.K. (2012b). Study of the association between the allelic variations in *DGAT1* gene with mastitis in Iranian Holstein cattle. *J. Mod. Genet.* **7(1),** 101-104.

Khatkar M., Thomson C., Tammen I. and Raadsma H.W. (2004). Quantitative trait loci mapping in dairy cattle: review and meta-analysis. *Genet. Sel. Evol.* **36,** 163-190.

Kühn C., Freyer G., Weikard R., Goldammer T. and Schwerin M. (1999). Detection of QTL for milk production traits in cattle by application of a specifically developed marker map of BTA6. *Anim. Genet.* **30,** 333-340.

Maddox J.F., Davies K.P., Crawford A.M., Hulme D.J., Vaiman D., Cribiu E.P., Freking B.A., Beh K.J., Cockett N.E., Kang N., Riffkin C.D., Drinkwater R., Moore S.S., Dodds K.G., Lumsden J.M., Van Stijn T.C., Phua S.H., Adelson D.L., Burkin H.R., Broom J.E., Buitkamp J., Cambridge L., Cushwa W.T., Gerard E., Galloway S.M., Harrison B., Hawken R.J., Hiendleder S., Henry H.M., Medrano J.F., Paterson K.A., Schibler L., Stone R.T. and Van Hest B. (2001). An enhanced linkage map of the sheep genome comprising more than 1000 loci. *Genome Res.* **11,** 1275-1289.

Madsen P. and Jensen J. (2002). A user's guide to DMU. A Package for Analyzing Multivariate Mixed Models. Danish Institute of Agricultural Sciences, Tjele, Denmark.

Martin P., Palhière I., Maroteau C., Bardou P., Canale-Tabet K., Sarry J., Woloszyn F., Bertrand-Michel J., Racke I., Besir H., Rupp R. and Tosser-Klopp G. (2017). A genome scan for milk production traits in dairy goats reveals two new mutations in Dgat1 reducing milk fat content. *Sci. Rep.* **7(1),** 1872.

Meuwissen T.H.E. and Goddard M.E. (1996). The use of marker haplotypes in animal breeding schemes. *Genet. Sel. Evol.* **28,** 161-176.

Meuwissen T.H.E. and Goddard M.E. (2001). Prediction of identity by descent probabilities from marker-haplotypes. *Genet. Sel. Evol.* **33,** 605-634.

Mohammad-Abadi M.R., Torabi A., Tahmourespoor M., Baghizadeh A., Esmailizadeh A.K. and Mohammadi A. (2010). Analysis of bovine growth hormone gene polymorphism of local and Holstein cattle breeds in Kerman province of Iran using polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP). *African J. Biotechnol.* **9(41),** 6848-6852.

Mohammadi A., Nassiry M.R., Mosafer J., Mohammad-Abadi M.R. and Sulimova G.E. (2009). Distribution of BoLA-DRB3 allelic frequencies and identification of a new allele in the Iranian cattle breed Sistani (*Bos indicus*). *Russian J. Genet.* **45(2),** 198-202.

Nadesalingam J., Plante Y. and Gibson J.P. (2001). Detection of QTL for milk production on chromosomes 1 and 6 of Holstein cattle. *Mamm. Genome.* **12,** 27-31.

Pasandideh M., Mohammad-Abadi M.R., Esmailizadeh A.K. and Tarang A. (2015). Association of bovine *PPARGC1A* and *OPN* genes with milk production and composition in Holstein cattle. *Czech J. Anim. Sci.* **60,** 97-104.

Ron M., Kliger D., Feldmesser E., Seroussi E. and Ezra E. (2001). Multiple quantitative trait locus analysis of bovine chromosome 6 in the Israeli Holstein population by daughter design. *Genetics.* **159,** 727-735.

Schnabel R.D., Sonstegard T.S., Taylor J.F. and Ashwell M.S. (2005). Whole-genome scan to detect QTL for milk production, conformation, fertility and functional traits in two US Holstein families. *Anim. Genet.* **36,** 408-416.

Sohrabi S.S., Esmailizadeh A.K., Babhizadeh A., Moradian H., Mohammad-Abadi M.R., Askari N. and Nasirifar E. (2012). Quantitative trait loci underlying hatching weight and growth traits in an F2 intercross between two strains of Japanese quail. *Anim. Prod. Sci.* **52(11),** 1012-1018.

Sorensen P., Lund M.S., Guldbrandtsen B., Jensen J. and Sorensen D. (2003). A comparison of bivariate and univariate QTL mapping in livestock populations. *Genet. Sel. Evol.* **35,** 605-622.

Szyda J., Liu Z., Maschka R. and Reents R. (2005). Computer system for routine QTL detection and genetic evaluation under a mixed inheritance model in dairy cattle. *Genet. Appl. Livest. Prod.* **33,** 249-250.

Velmala R.J., Vilkki K.T., Elo D.J., De Koning W. and Mäki-Tanila A.V. (1999). A search for quantitative trait loci for milk production traits on chromosome 6 in Finnish Ayrshire cattle. *Anim. Genet.* **30,** 136-143.

Wang T., Fernando R.L., van der Beek S. and Grossman M. (1995). Covariance between relatives for a marked quantitative trait locus. *Genet. Sel. Evol.* **27,** 251-274.

Weyrich A. (2012). Preparation of genomic DNA from mammalian sperm. *Curr. Protoc. Mol. Biol.* **2(13),** 1-3.