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소의 *CSRP3, APOBEC2*, Caveolin 유전자들의 단일염기다형 분석

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Analysis of SNPs in Bovine *CSRP3, APOBEC2* and Caveolin Gene Family

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요 약

CSRP3, APOBEC2, CAV1, CAV2 및 *CAV3* 유전자들은 포유동물에서 도체와 육질 형질에 중요한 역할을 하는 것으로 보고되고 있다. 따라서, 이 유전자들의 단일염기다형(Single nucleotide polymorphism; SNP)을 8개의 다른 소의 품종에서 확인한 결과 coding region에서 caveolin family 유전자에서 9개의 SNP, CSRP3유전자에서 1개의 SNP 및 APOBEC2 유전자에서 3개의 SNP가 존재함을 확인하였다. 이 coding region의 SNP들은 PCR-RFLP 방법에 의해 재확인하였으며 이들 유전자의 intronic region에서도 9개의 SNP가 존재함을 확인할 수 있었다. 8개의 다른 품종 소에 각 유전자들의 SNP들을 이용하여 유전자 빈도를 확인한 결과 *CAV2, CAV3, CSRP3* 및 *APOBEC2* 유전자의 SNP 중에서 5개가 품종간에서 유의적으로 차이가 있음을 확인할 수 있었다. 이 SNP들은 차후 검증작업을 통하여 육질관련 형질 마커로 이용될 수 있을 것으로 사료된다.

(**색인어** : 후보유전자, 단일염기다형, 육질형질, 대립유전자빈도)

Ⅰ. INTRODUCTION

Carcass and meat quality traits such as marbling, muscle tenderness, meat color and palatability are important to consumers and these factors ultimately determine the market value of beef. High levels of marbling improve the palatability and acceptability of beef by affecting the taste and tenderness of meat (Crouse et al., 1984). However, genetic improvement of carcass and meat quality traits by selective breeding is time consuming and expensive, and sometimes difficult to collect the trait data. Establishing genetic basis for variation in meat and carcass quality would likely an aid in the development of selection criteria to overcome these limitations.

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Polymorphisms in different candidate genes which are associated with variation in meat quality traits, especially marbling and tenderness, in cattle have been described previously. They include the genes encoding leptin (Schenkel et al., 2005; Shin and Chung, 2007a); DGAT1 (Thaller et al., 2003; Kong et al., 2007); TG (Barendse et al., 2004; Shin and Chung, 2007b) and GH1 (Barendse et al., 2006); TCAP (Cheong et al., 2007) for marbling, and CAPN1 (Page et al., 2002; White et al., 2005) and lysyl oxidase and calpastatin (Drinkwater et al., 2006) for tenderness. Haegeman et al. (2003) mapped and analyzed SNPs in thirteen bovine candidate genes for meat quality and carcass traits. In this study, we investigated 5 candidate genes namely *CAV1, CAV2* and *CAV3, CSRP3* and *APOBEC2*, whose effects in cattle or other species on carcass and meat quality traits have been reported previously.

The caveolin gene family has three members *CAV1, CAV2* and *CAV3*. Caveolins serve as markers and structural proteins for caveolae and their functions include intracellular trafficking of cellular components, lipid homeostasis and signal transduction. *CAV1* and *CAV2* are co-expressed in most cell types, but are enriched in adipocytes, endothelia and smooth muscle cells. In contrast, the expression of *CAV3* is muscle specific, primarily in skeletal and cardiac myocytes (Williams and Lisanti, 2004). *CAV1* is a cholesterol and major fatty acid binding protein (Murata et al., 1995). *CAV1* deficient mice are lean and resistant to diet induced obesity, have decreased white adipose tissue amount, loss of subcutaneous adipose tissue and abnormal abdominal fat pads (Razani et al., 2002). Mutations in the *CAV3* gene cause muscular dystrophy in human (McNally et al., 1998) and Zhu et al. (2006) reported *CAV3* gene might be a candidate gene of meat production traits in pig. *CSRP3* gene, also referred to as muscle LIM protein, has putative roles in skeletal muscle for regulation of myogenic differentiation (Lehnert et al., 2006) and this gene is closely located in QTL for hot carcass weight in cattle (Casas et al., 2003). Studies showed that *APOBEC2* gene express exclusively in heart and skeletal muscle (Liao et al., 1999) and is located in the marbling score QTL region on chromosome 23 in cattle (Casas et al., 2003). The objective of this study was to identify SNPs in 5 different genes and this in turn will help to examine associations of such polymorphisms with carcass and meat quality traits in cattle.

Ⅱ. MATERIAL AND METHODS

1. Sampling

A total of 212 samples from eight different cattle breeds (50 Hanwoo, 20 Hereford, 40 Limousine, 14 Angus, 30 Simmental, 20 Brahman, 12 Charolais, and 26 Brown Swiss) were used in this investigation. Blood samples were collected from National Institute of Animal Science, Korea, in a sampling tube containing heparin anti-coagulant and placed on ice for subsequent DNA extraction. Genomic DNA was extracted using QIAprep® Spin Miniprep Kit (Qiagen, USA) according to the manufacturer's instructions. Moreover, DNA samples of Limousin, Angus, Brown Swiss and Brahman breeds were collected from University of Adelaide, Adelaide, SA, Australia.

2. Primer design and DNA amplification

Eighteen primer pairs were designed using bovine sequence data from GenBank (accession numbers NC_007302, NC_007320, NC_007330 and NW_001494158). These primers used to amplify coding regions of candidate genes along with some parts of intron. The primer information, amplicon size and corresponding annealing temperatures are shown in Table 1. The PCR

Table 1. Primers, amplicon sizes and corresponding annealing temperatures for SNP typing of five different genes

Gene	Forward primer sequence (5' to 3')	Reverse primer sequence (5' to 3')	Amplicon size (bp)	Annealing temp (℃)
CAV1	GATCTTCCTTCCTCAGTTCC	AACATTCCTGCCTCCTCTTC	290	56
	TCGCTGCCAAGGCTAACT	CCTTACCTTGACCACGTCG	274	56
	TATTCCGAGTGAGGCTGATG	CAGGCAGTTGAGGTTGTTAG	835	52
	ACAACCTCAACTGCCTGTTC	CTGACAGTCTCACACAATGG	780	52
	GTGTGAGACTGTCAGAGTTG	GGACCAGCACTTGATTTG	667	52
CAV2	CTCTTCATGGACGACGACTC	AGAACATTCCGACGTCTCAG	681	60
	GGAGTATCCAACCTAGCGTG	CAGTTGCAGGCTGACAGAAG	541	52
CAV3	ACAGCCTTCTCCAGATGCAAC	TTGAAGACGTGATTGCGGAGC	733	60
	CTGGTGGATGGTCCTGTATG	CGGCAGGCTGAAGTTATG	488	56
CSRP3	AGCCTCTGATAGCAGTTGTG	GAGCATAACTTGAGCCTCCT	327	54
	CCATGATTGGTTCACTCTGG	CTGTCATGGTGTTCACATCC	228	54
	ACGCTCAAGGACAACTAC	GGAACAGAATGACCTACC	560	53
	ACTTGCTCAAGGTCACACAG	GATGAGTGGCTCCTAAGTGG	331	52
	CACTGCCTCAAGTCCAAGTT	CCTGGATCAGGATGAGAAGC	549	52
	AGCAACTGGCAGCCAGATTA	CACCAACATCCTCTGCACAA	702	52
APOBEC 2	CTTCCTGTCTCTGCTTCTGA	GGAGGTGTCACTCTGAGAAG	613	60
	CCGTTAGCATATAGGCAAGG	GAGACCACTCATTCCACCTG	768	60
	CAGGCATTCATTGAGGAAG	GGCTTGGTTCATAACCTGG	610	60

was carried out in a 25 µl reaction volume containing approximately 50 ng of genomic DNA, 1X PCR gold buffer (50 mM KCl, 10 mM Tris-HCl, pH 8.3), 1.5 mM $MgCl_2$, 200 µM dNTPs, 0.4 pM of each primer and 1 U Taq polymerase (Ampli Tag Gold™, Applied Biosystems, USA). The PCR amplification was performed in a GeneAmp 2700 (Applied Biosystems, USA) thermocycler with an initial denaturation at 94℃ for 10 min followed by 30~35 cycles of 30 sec at 94℃, 30 sec at specific annealing temperature for each primer set (see annealing temp. column in Table 1), 30 sec to 1 min at 72℃ and a final extension at 72℃ for 10 min. All the PCR products were run on agarose gels.

3. DNA sequencing and polymorphisms detection

Initially, twenty six animals from eight different breeds were used for direct sequencing of PCR amplicons. The PCR products were purified with Accuprep® PCR purification kit (Bioneer, Korea) according to the manufacturer's instructions. Sequencing reaction was performed by a 3100 automated DNA sequencer (Applied Biosystems, USA) using Big Dye Terminator Cycle Sequencing Ready Reaction Kit (v3.0, Applied Biosystems, USA). The samples showing ambiguous sequences in mixed condition were chosen for cloning using TOPO TA cloning kit (Invitrogen, UK). Besides, a total of 198

individuals from all eight breeds were used to detect PCR-RFLP restriction patterns for estimating the allele frequency. A set of restriction enzymes were used to digest PCR products of five candidate genes (Table 2). The resulting fragments were separated on 3 to 5% agarose gels stained with ethidium bromide and bands were visualized under UV light.

4. Bioinformatics

The sequence data were verified using Chromas program (ver. 1.41, McCarthy, 1997). DNA polymorphism was detected by comparing the sequence data with the sequences in the NCBI database (http://www.ncbi.nlm.nih.gov). Alignment of multiple sequences was performed with ClustalW program (Thompson et al., 1994) and mutations were scored using MEGA software (ver.3.1, Kumar et al., 2004). Translation of the nucleotide sequences into amino acids was performed using the Open Reading Frame Finder at NCBI (http://www.ncbi.nlm.nih.gov/gorf/gorf. html) for investigating the types of mutation. Allele frequencies of each SNP were compared by chi-square tests (χ^2) among the cattle breeds

Table 2. Polymorphisms identified in bovine caveolin gene family (*CAV1, CAV2* and *CAV3*), *CSRP3* and *APOBEC2* genes

Gene	Accession no.	SNP[a]	Location	Predicted amino acid change	Restriction enzyme
CAV1	NC_007302	g.33503A>G	Exon 3	Silent	*Rsa*I
		g.33782G>A	Exon 3	Silent	*Hinf*I
		g.34233G>A	Exon 3	Silent	*Ale*I/*Sfc*I
		g.34365G>A	Exon 3	Silent	None
CAV2	NC_007302	g.259C>T	Intron 1	Not applicable	None
		g.397A>G	Intron 1	Not applicable	None
		g.409C>T	Intron 1	Not applicable	*Rsa*I
		g.561A>C	Exon 2	Silent	None
		g.623G>T	Exon 2	Silent	*Fau*I
CAV3	NC_007320	g.86C>T	Exon 1	Silent	*Msp*I/*Hpa*II
		g.238A>G	Exon 1	Silent	*Nla*III
		g.29884C>T	Intron 1	Not applicable	*BsrB*I/*Aci*I
		g.29921A>G	Intron 1	Not applicable	*Bcc*I
		g.30122C>T	Exon 2	Silent	None
CSRP3	NC_007330	g.14859C>T	Exon 3	Silent	*Nla*III
		g.15000A>G	Intron 3	Not applicable	*Aci*I
		g.18555G>A	Intron 4	Not applicable	*Nla*III
		g.18582C>T	Intron 4	Not applicable	None
		g.18952A>G	Intron 4	Not applicable	None
APOBEC2	NW_001494158	g.1538417A>C	Exon 1	Silent	*Bfa*1
		g.1538747A>G	Exon 1	Silent	*Nci*I
		g.1547690C>T	Exon 2	Silent	*Hpy*CH4V

[a] Nucleotide positions are numbered according to the first base of each gene as it appears in GenBank.

using Minitab program (Minitab Inc., USA).

Ⅲ. RESULTS AND DISCUSSION

1. SNP identification

The sequence information obtained by direct sequencing of the PCR fragments was used to detect polymorphisms in meat and carcass quality related genes among the eight different cattle genotypes. The obtained sequences were compared with the sequences in the NCBI database. In total, 14 mutations were identified in caveolin gene family, 5 in *CSRP3* and 3 in *APOBEC2* gene. Details of all SNPs are presented in Table 2. We identified that all mutations in the coding regions of 5 candidate genes were silent. In *CAV1* gene, four A↔G transition mutations were detected at position g.33503A>G, g. 33782G>A, g.34233G>A and g.34365G>A in the exon 3 region and first 3 mutations were confirmed by restriction enzymes *Rsa*I, *Hinf*I and *Sfc*I, respectively. The enzymatic digestion created the following patterns in *CAV1* gene: 21+103+189+522 (allele A) and 21+292+522 (allele G) for *Rsa*I; 341+494 (allele G) and 146+341+348 (allele A) for *Hinf*I, and 99+295+386 (allele G) and 99+141+154+386 (allele A) for *Ale*I restriction endonuclease. The *Rsa*I restriction pattern for g.33503A>G substitution is shown in Fig. 1 (B). Five mutations were found in both coding and intronic region of *CAV2* gene and revealed two SNPs at position g.561A>C (no restriction site) and g.623G>T (*Fau*I cutting site) in the exon 2. Three other mutations were identified at position g.259C>T, g.397A>G and g.409C>T in the Intron 1 of this gene. But only one restriction site with *Rsa*I enzyme was observed at 409 bp and the T allele was cleaved into two fragments 92 and 305 bp, while C allele remained uncut as 397 bp due to the absence of *Rsa*I recognition site.

Three transition mutations were identified in the coding regions of *CAV3* gene at position g.86C>T (*Msp*I or *Hpa*II site) and g.238A>G (*Nla*III site) in exon 1, and g.30122C>T in exon 2(no restriction site). The restriction patterns were

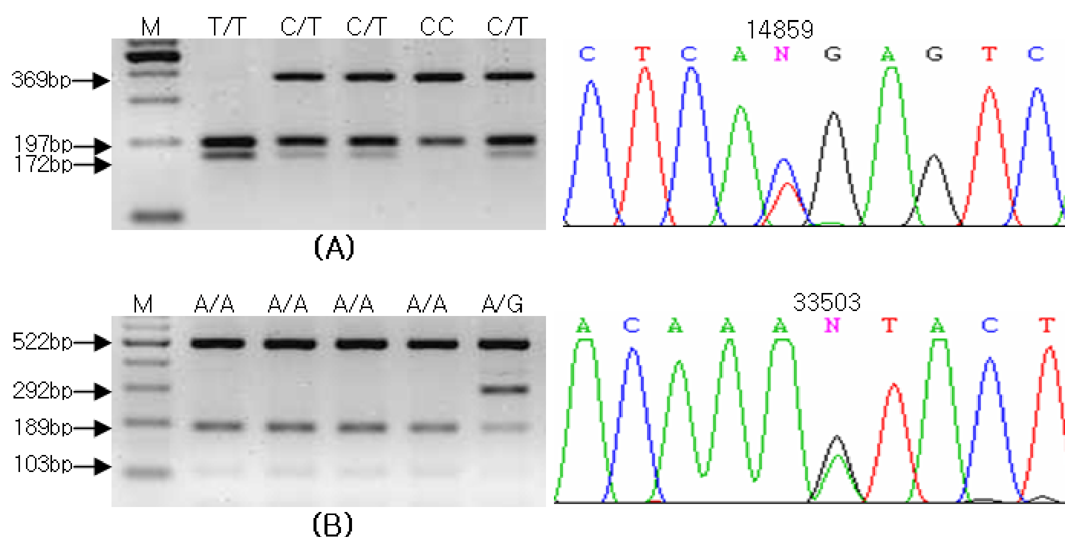

Fig. 1. PCR-RFLP patterns of two SNPs in bovine CSRP3 (A, *Nla*III) and CAV1(B, *Rsa*I) genes. Sequence chromatogram for the detection of a C>T substitution (above) at position 14859 in the exon 3 of CSRP3 and A>G substitution (below) at position 33503 in the exon 3 of CAV1 genes. M: 100bp molecular size marker.

17+85+279+351 (allele C) and 102+279+351 (allele T) for *Msp*I, and 236+497 (allele A) and 733 (allele G) for *Nla*III site. Furthermore, two other SNPs g.29884C>T (*BsrB*I and *Aci*I sites) and g.29921A>G (*Bcc*I site) were also found in the adjacent intronic 1 region of *CAV3* gene. In *CSRP3* gene, a transition mutation was detected at position g.14859C>T in the exon 3. The PCR-RFLP digestion patterns of this gene with *Nla*III enzyme are given in Fig. 1 (A) and the resulted restriction patterns were as follows: 369+191 (allele C) and 172+191+197 (allele T). In addition, 4 other SNPs were found at position g. 15000A>G (*Aci*I cutting site), g.18555G>A (*Nla*IV site), g.18582C>T (no restriction site) and g. 18952A>G (no restriction site), respectively in the intron 3 and 4 of *CSRP3* gene (Table 2). On the other hand, three SNPs were identified from the coding regions 1 and 2 of *APOBEC2* gene. These mutations were g.1538417A>C (creation of *Bfa*1 site), g.1538747A>G (*Nci*I site) and g. 1547690C>T (*Hpy*CH4V restriction site), respectively.

Several studies have been reported the molecular characterization and gene expression profiles of *CAV1* and *CAV2* in knock out mice (Scherer et al., 1996; Razani et al., 2002 and Lay et al., 2006); *CAV3* gene with pig (Zhu et al., 2006); *CSRP3* gene with cattle (Lehnert, et al., 2006) and *APOBEC2* gene with mouse and Human (Liao et al., 1999). However, there is no published report on SNPs of these five candidate genes in cattle except *CAV3*. We identified SNPs in these genes for the first time. Haegeman et al. (2003) found no mutation in the coding region of *CAV3* gene. They investigated SNPs among 11 European beef and dairy cattle breeds whereas only Charolais and Limousine breeds were common with our study. Breed differentiation might be one of the possible reasons for the inconsistent result compared to us.

2. Allele frequencies

Allele frequencies for the eight genotyped SNPs are shown in Table 3. The χ^2 test for differences in allele frequency among eight breeds was significant for five SNPs of *CAV2, CAV3, CSRP3* and *APOBEC2* genes. However, there was no significant allelic variation found for any SNP in the *CAV1* gene. In *CAV2* gene, the C allele frequency was significantly lower in Brahman breed (*Bos indicus*) compared to *Bos taurus* breeds (Simmental, Hereford, Limousine, Brown Swiss and Angus) ($P<0.001$) for g.409C>T) mutation. For g.29921A>G polymorphism in *CAV3* gene, the A-allele frequency was quite low in Brahman and Hanwoo breeds and allelic differentiation was highly significant among the cattle breeds ($P<0.001$). In *CSRP3* gene, Hanwoo and Hereford breeds tended to have a lower frequency of the C allele than the other cattle breeds ($P<0.001$). In addition, two SNPs (g.1538417A>C and g.1538747A>G) in *APOBEC2* gene showed reverse allele frequencies for A-allele in Brahman cattle and differed significantly between *Bos indicus* and *Bos taurus* breeds ($P<0.001$) and Hanwoo tended to have an intermediate allele frequencies for these two mutations. The allele frequencies for all mutations in Brown Swiss, a dairy breed, did not differ greatly from the other beef cattle breeds.

Studies showed that the allelic differentiation was significantly associated with meat and carcass quality traits in cattle (Buchanan et al., 2002; Schenkel et al., 2005; Shin and Chung, 2007). As an example, A252T SNP in the leptin gene, Schenkel et al. (2005) reported that the T allele was associated with less fat yield and grade fat and more lean yield compared with the A allele in crossbreds formed by several breeds. In the present study, the allelic discrimination that was significantly differed among different cattle breeds might have associations with meat quality traits and this also gave some hints for allelic distribution between *Bos indicus* and *Bos taurus* cattle

Table 3. SNP allele frequencies for caveolin gene family (*CAV1, CAV2* and *CAV3*), *CSRP3* and *APOBEC2* genes among eight different cattle breeds

Breed	*CAV1*	*CAV2*	*CAV3*	
	A33503G	C409T	C86T	A29921G
Hanwoo	A0.89/G0.11[a] (48)[b]	C0.60/T0.40 (39)	C0.95/T0.05 (28)	A0.36/G0.64 (35)
Limousine	A0.94/G0.06 (17)	C0.77/T0.23 (16)	C1.00/T0.00 (18)	A0.88/G0.12 (21)
Simmental	A0.84/G0.16 (19)	C1.00/T0.00 (20)	C0.82/T0.18 (17)	A0.88/G0.12 (21)
Hereford	A1.00/G0.00 (9)	C0.92/T0.08 (12)	C1.00/T0.00 (12)	A1.00/G0.00 (12)
Angus	A0.88/G0.12 (8)	C1.00/T0.00 (12)	C0.80/T0.20 (10)	A0.67/G0.33 (12)
Brahman	A0.87/G0.13 (12)	C0.16/T0.84 (16)	C0.83/T0.17 (12)	A0.50/G0.50 (12)
Charolais	A0.93/G0.07 (7)	C0.79/T0.21 (12)	C0.85/T0.15 (10)	A0.81/G0.19 (8)
Brown Swiss	–	C0.75/T0.25 (16)	C0.92/T0.08 (13)	A0.90/G0.10 (21)
Total	120	143	120	142
X^2 test (P value)	0.986	0.000	0.909	0.000

Breed	*CSRP3*		*APOBEC2*	
	C14859T	A15000G	A1538417C	A1538747G
Hanwoo	C0.35/T0.65 (42)	A0.91/G0.09 (23)	A0.34/C0.66 (50)	A0.43/G0.57 (50)
Limousine	C0.83/T0.17 (24)	A0.58/G0.42 (24)	A0.57/C0.43 (40)	A0.77/G0.23 (40)
Simmental	C0.78/T0.22 (20)	A0.57/G0.43 (20)	A0.56/C0.44 (25)	A0.58/G0.42 (25)
Herford	C0.54/T0.46 (12)	A0.79/G0.21 (12)	A0.60/C0.40 (20)	A0.70/G0.30 (20)
Angus	C0.79/T0.21 (12)	A0.83/G0.17 (12)	A0.82/C0.18 (14)	A0.93/G0.07 (14)
Brahman	C0.88/T0.12 (16)	A1.00/G0.00 (16)	A0.05/C0.95 (19)	A0.13/G0.87 (19)
Charolais	C0.75/T0.25 (12)	A0.62/G0.38 (12)	A0.88/C0.12 (12)	A0.83/G0.17 (12)
Brown Swiss	C0.83/T0.17 (24)	A0.65/G0.35 (24)	A0.50/C0.50 (26)	A0.77/G0.23 (26)
Total	162	143	206	206
X^2 test (P value)	0.003	0.054	0.000	0.000

[a] Allele frequencies indicated by number of adjacent base.
[b] The values in the parentheses indicate number of animals investigated.

breeds. However, we could not analyze trait specific association study due to shortage of samples from resource population.

Mutations in the gene's coding regions are particularly important in studies of the effects of SNPs on gene expressions and protein functions. Polymorphisms in the intronic regions are also significantly associated with production traits in cattle (Weikard et al., 2005; Li et al., 2004) and in pigs (Stinckens et al., 2007). Li et al. (2004) found significant allelic variation in the intron 2 of *Myf5* gene in two commercial beef lines for growth traits. We identified 13 silent mutations in the coding regions and 9 mutations in the introns of the 5 candidate genes. Moreover, significant differences in allele frequencies were detected both exon and intron between the different cattle breeds. Thus, the results of our study will be useful in a further search for association between polymorphisms in candidate genes studied and meat quality traits in cattle. However, further investigation with large number of samples from reference population will be necessary to find the associations between the identified SNPs and meat quality traits.

Ⅳ. ABSTRACT

The cysteine and glycine rich protein 3 (*CSRP3*), apolipoprotein B mRNA editing enzyme catalytic polypeptide like 2 (*APOBEC2*) and caveolin (*CAV*) gene family (*CAV1, CAV2, CAV3*) have been reported to play important roles for carcass and meat quality traits in pig, mouse, human and cattle. As an initial step, we investigated SNPs in these 5 genes among eight different cattle breeds. Eighteen primer pairs were designed from bovine sequence data of NCBI database to amplify the partial gene fragments. Sequencing results revealed 9 SNPs in the coding regions of three caveolin genes, 1 SNP in *CSRP3* and 3 SNPs in *APOBEC2* gene. All the identified SNPs were confirmed by PCR-RFLP. Also, 9 more intronic SNPs were detected in these genes. However, all identified mutations in the coding region do not change amino acid sequence. Allelic distributions were significantly different for 5 SNPs in *CAV2, CAV3, CSRP3* and *APOBEC2* genes among the eight different breeds. These results gave some clues about the polymorphisms of these genes among the cattle breeds and will be useful for further searches for identifying association between these SNPs and meat quality traits in cattle.

(**Key words** : Candidate gene, Single Nucleotide Polymorphism (SNP), Meat quality traits, Allele frequency)

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