Asian-Aust. J. Anim. Sci.
Vol. 20, No. 11 : 1662 - 1669
November 2007

www.ajas.info

Molecular Cloning and Characterization of Bovine HMGA1 Gene

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ABSTRACT : The high mobility group AT-hook1 (HMGA1) proteins are known to be related to the regulation of gene transcription, replication and promotion of metastatic progression in cancer cells. The loss of expression by disrupting the HMGA1 gene affects insulin signaling and causes diabetes in the mouse. Previously identified single nucleotide polymorphism (SNP) of HMGA1 was significantly associated with fat deposition traits in the pig. In this study, we identified 3,935 bp nucleotide sequences from exon 5 to exon 8 of the bovine HMGA1 gene and its mRNA expression was observed by quantitative real-time PCR. Six single nucleotide polymorphisms in the bovine HMGA1 gene were detected and the allele frequencies of these SNPs were investigated using the PCR-RFLP method in nine cattle breeds including Limousin, Simmental, Brown Swiss, Hereford, Angus, Charolais, Hanwoo, Brahman and Red Chittagong cattle. The map location showed that the bovine HMGA1 gene was also closely located with a previously identified meat quality QTL region indicating this gene is the most likely positional candidate for meat quality traits in cattle. (**Key Words:** HMGA1, SNP, Meat Quality Traits, Cattle)

INTRODUCTION

High mobility group (HMG) proteins, which are known as nonhistone nuclear protein, are related to change of DNA structure and chromatin organization by DNA activities such as transcription, replication, and recombination (Bustin, 1999). These proteins are subdivided into three families by functional sequence motifs that consist of HMGA including AT-hook motif, HMGB including HMG-box motif and HMGN containing nucleosomal binding domain. Among these three families, the mammalian HMGA gene family is composed of HMGA1 (HMGI/Y) and HMGA2 (HMGI-C) (Reeves, 2001; Murua Escobar et al., 2005). The HMGA1 gene produces 1a (HMGI) and 1b (HMGY) through alternative splicing transcript variants. The HMGA1 proteins have modification sites, such as acetylation and phosphorylation, and three AT-hooks peptide motifs that bind protein-DNA or protein-protein interaction to minor groove with AT-rich regions that are known as binding important element to chromatin (Reeves, 2001). Moreover, HMGA1a and HMGA1b proteins interact with C/EBP (CAAT/enhancer-binding protein) involved adipocyte differentiation *in vivo* and *in vitro* and the protein expression was increased when the cells become adipocytes from preadipocytes. Therefore, these proteins play important roles in adipocytic cell growth and differentiation (Melillo et al., 2001). Recently, Foti et al. (2005) identified that reduction of HMGA1 expression in human and loss of expression by disrupting HMGA1 gene in mouse causes insulin resistance and diabetes from controlling glucose homeostasis. In pig, Kim et al. (2004; 2006) suggested that single nucleotide polymorphisms (SNPs) of HMGA1 gene were significantly associated with fat deposition traits and polymorphisms between MC4R (melanocortin 4 receptor) and HMGA1 were related to growth, fatness, and lean meat contents in commercial pigs. In this study, we reported the single nucleotide polymorphisms (SNPs) and their allele frequencies in nine cattle breeds as an initial step for identifying the relationships between HMGA1 and fat related traits in cattle.

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Received March 14, 2007; Accepted June 10, 2007

MATERIALS AND METHODS

Genomic DNA and total RNA preparations

Blood samples were collected from seven *Bos taurus*

Table 1. Primer information for identification of chromosome location and polymorphisms of the bovine HMGA1 gene

Primer name	Primer sequence (5' - 3')	Amplified region	Annealing Temp (°C)	Location of SNP (bp)	Restriction enzyme
E5F	GGAAGATGAGCGAGTCGAGC	Exon 5	63		
E6R	AGGTGTTGGCACTTCACTGG	Exon 6			
E6F	CCAGTGAAGTGCCAACACCT	Exon 6	63		
E7R	CTCCCTGGAGTTGTGGTGGT	Exon 7			
E7F	CACCACAACTCCAGGGAGAGA	Exon 7	63		
E8R	CTTCCTCTGAGGACTCCTGC	Exon 8			
RH F	CATAGCCTGTTGGGTGGGAG	Intron 7	60		
RH R	ATGTCGGGACACCACACAGG	Intron 7			
SNP1F	ACCTTTGCCTCGGTTTACCT	Intron 5	56	301	*Hinf*I
SNP1R	CAATACGCTGGTCCACAATG	Intron 5			
SNP2F	ATGTAAGCCCAGCAGTACGC	Intron 5	63	719	*Bst*NI
SNP2R	GTCACTCTGCCACCAACTCC	Intron 5			*Hpy*CH4Ⅳ, *Hpy*CH4Ⅴ
SNP3R	GGCACATCAGTGGTGTTTCC	Intron 5	63	810,952	*Bbs*I
SNP4F	CCTGTTCACGTGTGGAGAAG	Intron 5	63	1,301	
SNP4R	ACCTGCAAACCAGACTCCCT	Intron 5			
SNP5R	CCAGAATCCACAGGAACCAT	Intron 5	63	1,432	*Nla*Ⅳ

(Limousin, Simmental, Brown Swiss, Hereford, Angus, Charolais, Hanwoo) and two *Bos indicus* (Brahman and Red Chittagong Bangladesh indigenous cattle) breeds. These samples were collected in tubes containing heparin anticoagulant and suspended in a red blood cell (RBC) lysis buffer. White cells were collected by centrifugation and genomic DNA was extracted using DNeasy blood and tissues kit (QIAGEN, Germany). For total RNA preparation, samples from skeletal muscle tissues, heart, spleen, liver and kidney were taken from four Hanwoo (Korean cattle) within 20 min of dissection. The sampled tissues were cut into small pieces and immediately emerged into liquid nitrogen and then stored in a -70°C fridge until use. Total RNA from each sample tissue was isolated using RNeasy mini kit (QIAGEN, Germany) and the concentrations and purities were measured by spectrophotometer.

Primer designs and determination of gene organization

Primers (Table 1) were designed based on assembled EST sequences (TC317594) from TIGR database (http://www.tigr.org) to amplify the bovine HMGA1 gene by polymerase chain reaction (PCR). The final composition of PCR reaction consisted of 50 ng bovine genomic DNA, 1× PCR buffer, 0.4 M primers, 0.2 mM each dNTP, 1.5 mM $MgCl_2$ and 1 U *Taq* polymerase (Applied Biosystems, USA) in total volume of 25 μl. The thermal profiles included an initiation denaturation at 94°C for 10 min, following 35 cycles of denaturation at 94°C for 30 sec, annealing at 63°C for 30 sec and extension at 72°C for 1 min 30 sec, then a final extension step at 72°C for 10 min using PTC-200 programmable thermal controller (MJ Research, USA). The PCR products were ligated in the pGEM-T easy vector (Promega, USA) and sequences were determined using Applied Biosystems dye terminator sequencing kit on an ABI 3700 DNA analyzer (Applied Biosystems, USA).

Bioinformatics

Nucleotide BLAST programs of NCBI (http://www.ncbi.nlm.nih.gov/BLAST/) were used for sequence homology searches in public databases (Altschul et al., 1990). A search for open reading frame (ORF) and translation of the nucleotide sequences into the amino acids was performed using the open reading frame finder at NCBI (http://www.ncbi.nlm.nih.gov/gorf/gorf.html). Multiple sequence alignment was performed with the ClustalW program (Thompson et al., 1994) and shading of the aligned sequences was achieved using the GeneDoc program version 2.6.02 (http://www.psc.edu/biomed/genedoc/). A neighbor-joining (NJ) phylogenetic tree was constructed using MEGA 3.0 (Kumar et al., 2004) based on genetic distances calculated with Kimura's two-parameter method.

Radiation hybrid mapping

A 318 bp PCR product containing part of intron 7 of the bovine HMGA1 gene was obtained using RH-F and RH-R primers (Table 1). The PCR product was sequenced to confirm the amplification of target PCR product. Radiation hybrid (RH) mapping was performed using the 5000-rad bovine radiation hybrid panel (Womack et al., 1997) and analyzed using RHMAPPER program (Slonim et al., 1997), which is located at the interpreting web pages at Texas A & M University (http://bovid.cvm.tamu.edu/cgi-bin/rhmapper.cgi). The 318 bp PCR product was amplified in a reaction containing 25 ng template DNA, 1× PCR buffer, 0.4 M primers, 0.2 mM each dNTP, 1.5 mM $MgCl_2$ and 1 U *Taq* polymerase (Applied Biosystems, USA) in total volume of 25 μl. The thermal profiles included an initiation denaturation at 94°C for 10 min, following 35 cycles of denaturation at 94°C for 30 sec, annealing at 60°C for 30 sec and extension at 72°C for 30 sec and then a final extension step at 72°C for 10 min using a PTC-200

programmable thermal controller (MJ Research, Inc., USA).

Quantitative real-time PCR

Single-stranded cDNA was synthesized from 1 μg total RNA from four different individuals extracted from heart, liver, spleen, round muscle and loin. Initially, RNA was denatured at 70°C for 10 min and reverse transcription was performed in reactions containing 5 mM $MgCl_2$, 10 mM Tris-HCl (pH 9.0), 50 mM KCl, 0.1% Triton® X-100, 1 mM each dNTP, 0.5 unit Recombinant RNasin® Ribonuclease Inhibitor, 15 unit AMV Reverse Transcriptase (Promega, USA) and 500 ng Oligo(dT)15 primer at 42°C for 1 h.

Quantitative real-time PCR was performed in three replicates using Rotor Gene 2000 PCR machine and analyzed using Rotor Gene 2000 program version 6.0 (Corbett Research, Australia). GAPDH (glyceraldehyde-3-phosphate dehydrogenase) gene was used as an internal control. The thermal profile included 25 cycles of denaturation 94°C for 30 sec, annealing at 60°C for 30 sec and extension at 72°C for 3 min.

Polymorphisms and allele frequencies

The SNPs in the bovine HMGA1 gene were initially screened by sequencing 5 regions of the gene in 29 animals taken from 5 breeds. The identified SNPs were confirmed by restriction fragment length polymorphisms (RFLPs) using *Hinf*I (PCR products using primers SNP1F and SNP1R), *Bst*NI (PCR products using primers SNP2F and

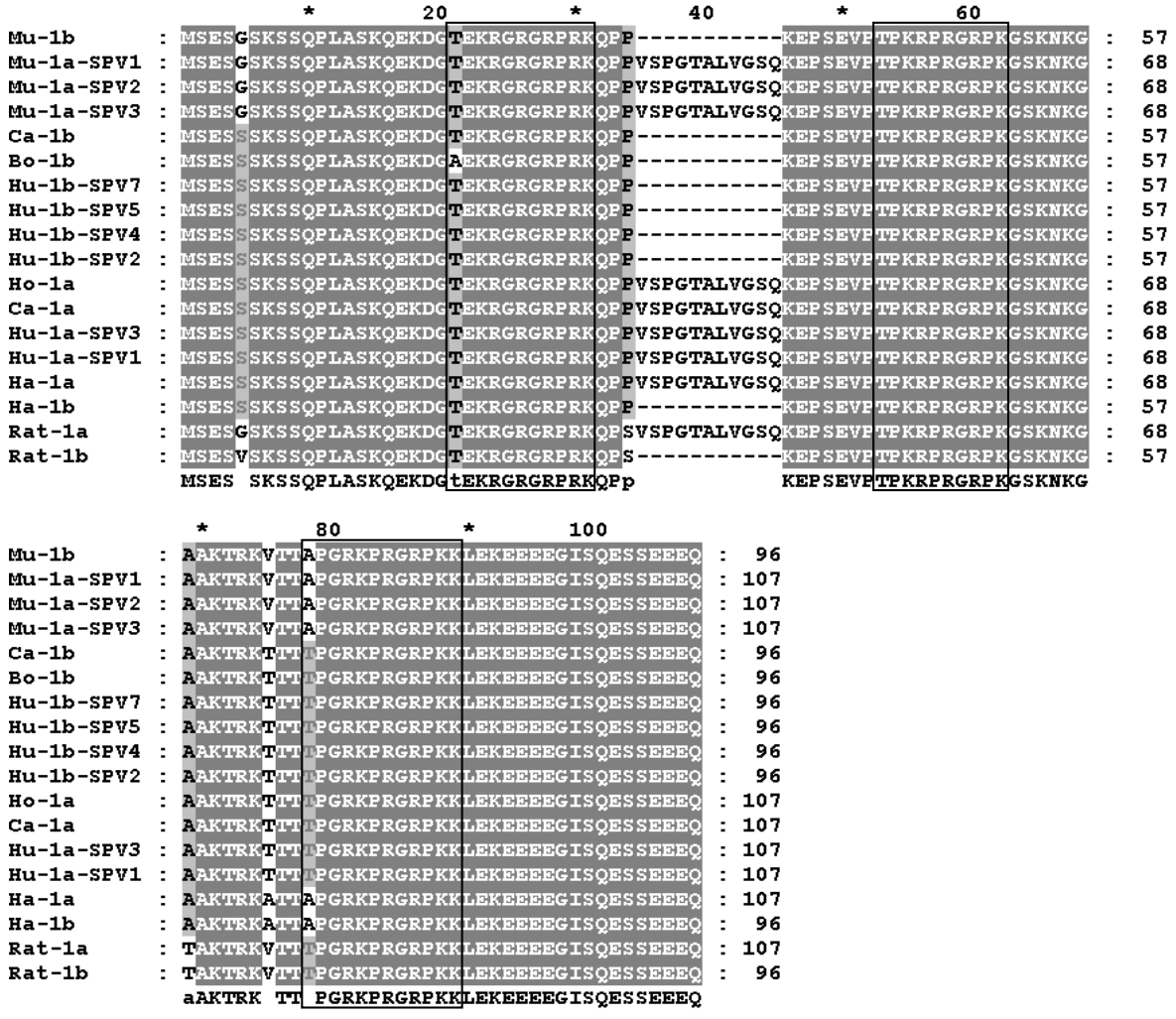

Figure 1. Comparisons of deduced HMGA1 amino acid sequences of known mammalian species. The shading indicates the degree of similarity. Three AT-hook motifs are shown as boxes. Mu-1b: mouse HMGA1b, Mu-1a-SPV1: mouse HMGA1a transcript variant 1, Mu-1a-SPV2: mouse HMGA1a transcript variant 2, Mu-1a-SPV3: mouse HMGA1a transcript variant 3, Ca-1b: canine HMGA1b, Bo-1b: bovine HMGA1b, Hu-1b-SPV7: human HMGA1b transcript variant 7, Hu-1b-SPV5: human HMGA1b transcript variant 5, Hu-1b-SPV7: human HMGA1b transcript variant 7, Hu-1b-SPV2: human HMGA1b transcript variant 2, Ho-1a: horse HMGA1a, Ca-1a: canine HMGA1a, Hu-1a-SPV3: human HMGA1a transcript variant 3, Hu-1a-SPV1: human HMGA1a transcript variant 1, Hu-1a: human HMGA1a, Ha-1a: hamster HMGA1a, Ha-1b: hamster HMGA1b, Rat-1a: rat HMGA1a, Rat-1b: rat HMGA1b.

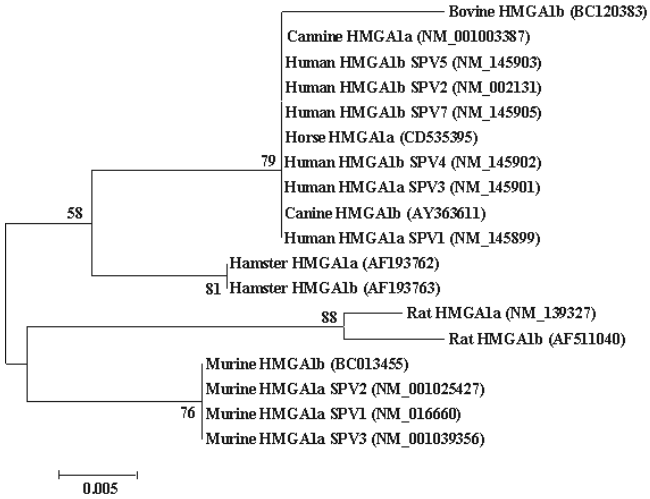

Figure 2. Phylogenic tree based on the amino acid sequences of the HMGA1a and HMGA1b genes. The percentage numbers at nodes indicate the levels of bootstrap support based on neighbor-joining analyses of 1,000 resampled data sets. The scale bars indicate 0.005 amino acid substitutions per each amino acid position.

SNP2R), *Hpy*CH4IV (PCR products using primers SNP2F and SNP3R), *Hpy*CH4V (PCR products using primers SNP2F and SNP3R), *Bbs*I (PCR products using primers SNP4F and SNP4R) and *Nla*IV (PCR products using primers SNP4F and SNP5R) restriction enzymes (New England Labs, USA) and allele frequencies were calculated in total 248 animals from 7 *Bos taurus* (Limousin, Simmental, Brown Swiss, Hereford, Angus, Charolais, Hanwoo) and 2 *Bos indicus* (Brahman, Red chittagong cattle) breeds.

RESULTS AND DISCUSSION

Characterization of the bovine HMGA1 gene

In order to initial amplify of the bovine HMGA1 gene, primers (E5F, E6R, E6F, E7R, E7F and E8R) were designed from assembled EST sequences of TIGR database. After sequencing of the PCR product, putative intron sizes were predicted from alignment between human (GenBank accession no. L17131) and bovine sequences. Therefore, the partial bovine HMGA1 gene from exon 5 containing start codon to exon 8 was amplified using three overlapping fragments. The first fragment was 1.8 kb and contained from exon 5 to exon 6. The 2nd and 3rd PCR products were 1.3 kb contained intron 5 to exon 8. As a result, A total 3,935 bp nucleotides consisted four exons and three introns was obtained and the sequencing result has been deposited at GenBank (accession no. DQ280380). Each exon/intron boundaries conformed to GU-AG rule with splice donor and acceptor consensus sequences. Comparison between this sequence and *Bos taurus* chromosome 23 contig sequence generated by the Balyor College of Medicine Human Genome Sequencing Center at NCBI (accession no. NW_930179) showed 99% significant sequence similarity. However, 33 bp nucleotides (nucleotide position 36390-36422) of HMGA1 intron 7 in chromosome 23 contig sequences at NCBI were not existed, therefore the result indicates that either the bovine draft sequences (Build 2.1) have an assembling error in this gene or the animal used for the bovine genome sequencing has a 33-bp deletion in intron 7 of the bovine HMGA1 gene.

Previously, Reeves (2001) reported that human HMGA1 gene consisted of 8 exons and expressed 2 variant transcripts, including HMGA1a and HMGA1b, by alternative splicing in exon 5. Moreover, four functional promoter/enhancer regions from exon 1 to 4 by transcription factors (eg. AP-1, c-myc, etc) or several growth factors (eg. TGF-α, PDGF, FGF etc) in tumor cell lines were induced expression of coding region from exon 5 to 8 of HMGA1 gene (Reeves and Beckerbauer, 2001). Amino acid similarity of known mammalian species, including human HMAG1a transcript variant 1 and 3 (Johnson et al., 1989) and HMGA1b transcript variant 2, 4, 5, 7 (Johnson et al., 1989), canine HMGA1a and 1b (Murua Escobar et al., 2004), horse HMGA1a (Vandenplas et al., 2003), hamster HMGA1a and 1b (Aldrich et al., 1999), rat HMGA1a and 1b (Bussemakers et al., 1991; Sgarra et al., 2002), mouse HMGA1a transcript variant 1, 2 and 3 (Johnson et al., 1988), 1b (Strausberg et al., 2002), bovine HMGA1b (Moore et al., 2006), showed significant sequence homologies between 94 to 98% (Figure 1). Of these sequences, transcript variants in human and mouse were separated by 5' UTR (untranslated region) sequence. In other word, the sequences in the coding region were the same. Also the sequence indicated that DNA-binding motifs in HMGA1 gene have three AT-hooks (Figure 1) that associate with minor groove of the B-form DNA (Banks et al., 1999).

In order to identify relationships of the HMGA1a and HMGA1b genes in 7 mammalian species, the sequences were aligned and NJ phylogenetic tree was constructed. Based on the result, cattle were more closely related with human, canine and horse HMGA1a and HMGA1b gene (Figure 2).

Radiation hybrid mapping

To map the chromosomal location of bovine HMGA1 gene, 5000-rad bovine radiation hybrid panel was used. The most significantly linked marker was identified as BAK1 on BTA23 (Everts-van der Wind et al., 2004). Before investigating of the chromosomal location, the bovine HMGA1 gene was not reported in public database. However, the bovine HMGA1 gene was recently identified

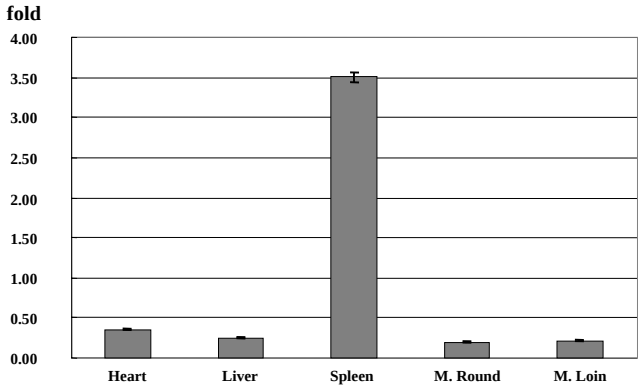

Figure 3. Result of the bovine HMGA1 expression pattern using quantitative real-time PCR. The gene expression levels were normalized to the expression level of GAPDH as an internal control.

on BTA 23 from 7,982,051 to 7,986,031 bp in UCSC Genome Browser (Btau_2.0; http://genome.ucsc.edu/). The sequence and map location were well matched indicating the reliability of the bovine genome sequence. The chromosomal location of the HMGA1 gene in the bovine genome contains slaughter and hot carcass weight QTLs (quantitative trait loci) reported by Kim et al. (2003). In addition, Casas et al. (2003) identified a marbling score QTL between microsatellite markers BM1258 and BMS468 which contains the bovine HMGA1 gene location. Also, the porcine comparative chromosomal location of HMGA1 gene were previously identified on chromosome 7 associated with IMF content and fat deposition QTLs, where the comparative map location of bovine HMGA1 gene (Bidanel et al., 2002; Kim et al., 2004; Zuo et al., 2004). Therefore, we suggest that the bovine HMGA1 gene is a very strong positional candidate gene for the meat quality related quantitative traits in cattle.

Expression profile of the bovine HMGA1 gene

The mRNA expression of the bovine HMGA1 gene was investigated using quantitative real-time PCR from heart, liver, spleen, round muscle and loin using primer E5F and E8R (Table 1). The highest mRNA expression was observed in spleen (Figure 3). Chiappetta et al. (1996) reported that mRNA expression pattern of the human and mouse HMGA1 gene was detectable at very low levels in adult tissues whereas it was abundantly expressed in embryonic tissues. High level of HMGA1 expression was observed in canine spleen, indicating the similar result was obtained in our study.

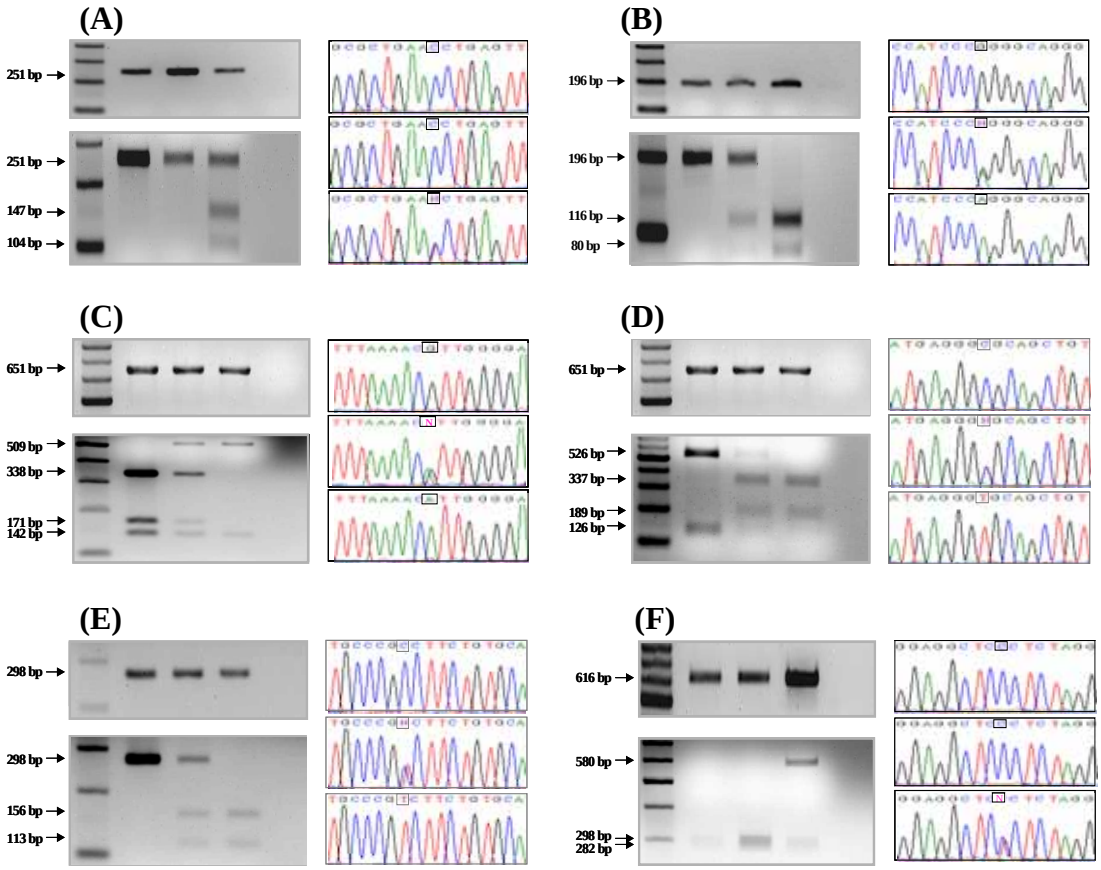

Figure 4. PCR-RFLP and sequencing results of six SNPs in bovine HMGA1 gene. (A) SNP at nt 301, (B) SNP at nt 719, (C) SNP at nt 810, (D) SNP at nt 952, (E) SNP at nt 1301, (F) SNP at nt 1432.

Table 2. Allele frequencies for the six SNPs identified in bovine HMGA1 gene among nine different breeds

Breeds	No. of Animals	C301T[a]	A719G	A810G	T952C	T1301C	C1432T
Limousin	37	C1.00/T0.00	A0.92/G0.08	A0.99/G0.01	T0.93/C0.07	T0.96/C0.04	C1.00/T0.00
Simmental	23	C1.00/T0.00	A0.83/G0.17	A0.87/G0.13	T0.83/C0.17	T0.87/C0.13	C1.00/T0.00
Brown Swiss	24	C1.00/T0.00	A0.75/G0.25	A0.90/G0.10	T0.88/C0.12	T0.90/C0.10	C0.90/T0.10
Hereford	18	C1.00/T0.00	A0.89/G0.11	A1.00/G0.00	T0.89/C0.11	T1.00/C0.00	C1.00/T0.00
Angus	13	C1.00/T0.00	A0.85/G0.15	A1.00/G0.00	T0.92/C0.08	T1.00/C0.00	C1.00/T0.00
Charolais	12	C1.00/T0.00	A0.67/G0.33	A0.96/G0.04	T0.75/C0.25	T0.92/C0.08	C1.00/T0.00
Hanwoo (Native Korean)	49	C0.91/T0.09	A0.65/G0.35	A1.00/G0.00	T0.81/C0.19	T0.96/C0.04	C0.91/T0.09
Brahman	20	C1.00/T0.00	A0.20/G0.80	A0.27/G0.73	T0.22/C0.78	T0.25/C0.75	C1.00/T0.00
Red chittagong (Native Bangladesh)	52	C1.00/T0.00	A0.12/G0.88	A0.31/G0.69	T0.13/C0.87	T0.28/C0.72	C1.00/T0.00

[a] Allele frequencies indicated by number adjacent to base.

SNPs of bovine HMGA1 gene

To identify SNPs of the bovine HMGA1 gene, genomic fragments were amplified using nine primer sets (Table 1) based on 3,935 bp nucleotide sequences in 29 animals from 5 breeds (Jersey, Limousin, Hereford, Angus, Hanwoo). The PCR products were bidirectionally sequenced and aligned. The results identified total 6 SNPs in intron 5, C310T, A719G, A810G, T952C, T1301C and C1432T (Table 2) and confirmed by *Hinf*I, *Bst*NI, *Hpy*CH4IV, *Hpy*CH4V, *Bbs*I and *Nla*IV PCR-RFLP analyses respectively (Figure 4). Recently, Kim et al. (2006) reported that HMGA1 gene polymorphism in intron 6 was related to growth, fatness and lean meat content in pigs indicating these SNPs are the possible markers for meat quality traits in cattle.

Allele frequencies of bovine HMGA1 SNPs were also investigated using PCR-RFLP tests in total 248 animals from 7 *Bos taurus* and 2 *Bos indicus* breeds. The results showed four SNPs (A719G, A810G, T952C, T1301C) had high differences in allele frequencies between *Bos taurus* and *Bos indicus* breeds, may indicating the different selection was applied between *Bos taurus* and *Bos indicus* breeds.

Previously HMGA1 variation in pigs showed an association with meat quality traits. We first report the polymorphisms of the bovine HMGA1 gene in different cattle breeds. Other researchers have identified the relationships between phenotypic traits and SNPs in the candidate genes (Chung et al., 2005; Cheong et al., 2006; Kong et al., 2006; Shin and Chung, 2007a; b; c; Shin et al., 2007; Kong et al., 2007). Utilization of these polymorphisms could be useful for marker assisted selection for better quality meat producing cattle in the future. Further detailed investigation is ultimately needed for more clarification about the HMGA1 gene polymorphisms and its associated functions.

ACKNOWLEDGEMENT

This work was supported by a grant (Code # 20070401034031) from Biogreen 21 program, Rural Development Administration, Republic of Korea and by the ERC program of KOSEF (grant R11-2002-100-00000-0). We gratefully acknowledge provision of bovine radiation hybrid panel by Prof. James Womack, Texas A & M University, USA. We also thank to Prof C. D. K. Bottema for providing valuable bovine DNA samples.

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