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# Identification of Candidate SNP (Single Nucleotide Polymorphism) for Growth and Carcass Traits Related to QTL on Chromosome 6 in Hanwoo (Korean Cattle)*

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**ABSTRACT :** As genetic markers, single nucleotide polymorphisms (SNP) are very appropriate for the development of genetic tests for economic traits in livestock. Several microsatellite markers have been identified as useful markers for the genetic improvement of Hanwoo. Among those markers, ILSTS035 was recently mapped at a similar position with four SNPs (AH1_11, AH1_9, 31465_446, and 12273_165) in a linkage map of EST-based SNP in BAT6. Among the four SNPs, two SNPs (31465_446 and 12273_165) were analyzed using BLAST at the NCBI web site. The sequences including the 12273_165 SNP were identified at the intron region within the LOC534614 gene on the gene sequence map (*Bos taurus* NCBI Map view, build 3.1). The LOC534614 gene represents a protein similar to myosin heavy chain, fat skeletal muscle, embryonic isoform 1 in the dog, and myosin_1 (Myosin heavy chain D) in *Macaca mulatta*. In cattle, the myosin heavy chain was associated with muscle development. The phenotypic data for growth and carcass traits in the 415 animals were analyzed by the mixed ANCOVA (analysis of covariance) linear model using PROC GLM module in SAS v9.1. By the genotyping of Hanwoo individuals (n = 415) to evaluate the association of SNP with growth and carcass traits, it was shown that the 12273_165 SNP region within LOC534614 may be a candidate marker for growth. The results of the statistical analyses suggested that the genotype of the 12273_165 SNP significantly affected birth weight, weight of the cattle at 24 months of age, average daily gain and carcass cold weight ($p<0.05$). Consequently, the 12273_165 SNP polymorphisms at the LOC534614 gene may be associated with growth in Hanwoo, and functional validation of polymorphisms in LOC534614 should be performed in the future. (**Key Words :** SNP, QTL, BTA6, Growth, Hanwoo)

## INTRODUCTION

A major goal of cattle genome research is to identify quantitative trait loci (QTL) that affect economically relevant traits in livestock. Over several years, QTL studies of economic traits have been conducted and the underlying genetic variation in QTL was identified via molecular means for successful marker-assisted selection in livestock. Microsatellite markers have been previously utilized to identify QTL that affect traits. A high density bovine genetic map was developed by two groups in Japan and the USA, based on 3,802 microsatellite markers (Ihara et al., 2004). However, this map has limited applicability, due to the difficulties of transferring the technology to target herds. Currently, by increasing genomic DNA sequence information, several single nucleotide polymorphism (SNP) markers have been developed for the mapping of specific targeted genes (Thue et al., 2004) or positional candidate genes proximal to QTL (Connor et al., 2004). The high density linkage map connecting SNPs information on genetic markers may provide a valuable resource for gene based QTL study (Snelling et al., 2005). Recent studies in humans and mice have shown that SNP markers may have the potential to track functional alleles on the basis of the genotypes of individuals without the need to reproduce pedigree studies within the target population (Reich et al., 2001; Wiltshire et al., 2003). In the Hanwoo population,

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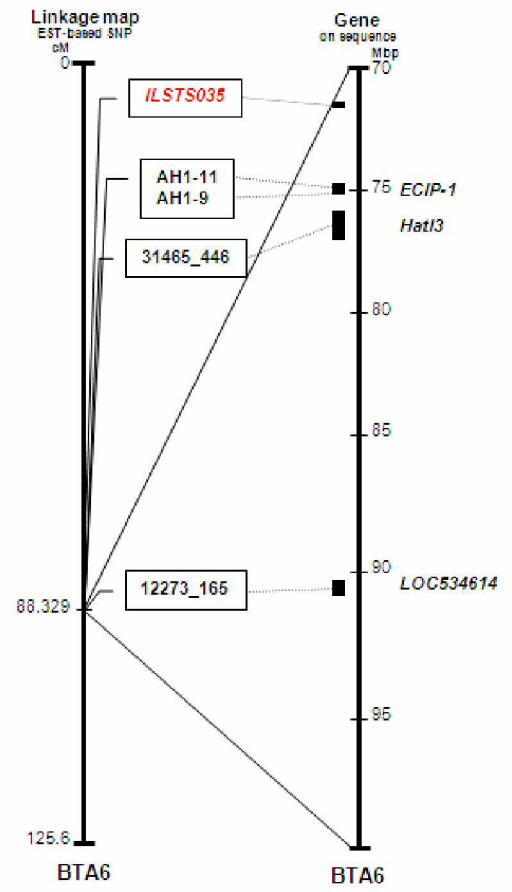


**Figure 1.** Alignment of 4 SNP (AH1_11, AH1_9, 31465_446 and 12273_165) on linkage map of EST-based SNP (Snelling et al., 2005) and Gene on sequence map (NCBI Map viewer) in BTA6.

Kim et al. (2003) first conducted linkage mapping to detect QTL that influenced daily gain and marbling score which thereby suggested that 11 microsatellite loci on bovine chromosome 6 were associated with the economic traits.

This study compared 11 QTL for the Hanwoo QTL research of Kim et al. (2003) with an EST-based linkage map including microsatellites (Snelling et al., 2005) and identified the ILSTS035 microsatellite, which was located in a similar position to four SNPs (AH1_11, AH1_9, 31465_446 and 12273_165) on the EST-based linkage map. These four SNPs were also identified from the EST sequence including SNP, which was arranged on the gene sequence with the NCBI Mapviewer. Thus, the AH1_11 and AH1_9 SNP were contained in the ECIP-1 gene and the 31465_446 SNP in the Hatl3 gene. However, the 12273_165 SNP was contained in the LOC534614 gene, which had yet to be identified (Figure 1). Thus, the principal objective of this study was to evaluate the association of the four SNP on an EST-based linkage map with economic traits for growth and carcass traits in Hanwoo (Korean cattle).

**Table 1.** Phenotypic values for growth and carcass traits in Korean cattle (n = 415)

| Traits[1] | Average | SD |
|---|---|---|
| Growth | | |
| BW (kg) | 25.30 | 1.59 |
| WT9 (kg) | 221.03 | 42.96 |
| WT15 (kg) | 344.29 | 43.73 |
| WT18 (kg) | 415.51 | 48.55 |
| WT24 (kg) | 568.60 | 58.82 |
| ADG (kg) | 0.752 | 0.09 |
| Carcass | | |
| CWT (kg) | 316.75 | 34.50 |
| BF (mm) | 7.66 | 3.05 |
| LMA ($cm^2$) | 75.31 | 8.12 |
| MS | 4.93 | 4.02 |

[1]BW = Birth weight, WT9 = Weight at 9 months, WT15 = Weight at 15 months, WT18 = Weight at 18 months, WT24 = Weight at 24 months, ADG = Average daily gain, CWT = Carcass cold weight, BF = Backfat thickness, LMA = *Longissimus dorsi* muscle area, MS = Marbling score.

## MATERIALS AND METHODS

### Animals and phenotype data

The Hanwoo population was reared under the progeny-testing program of the National Livestock Research Institute (NLRI) of Korea. All steers of the national progeny-testing population were fed under the tightly controlled conditions of the feeding program and the average of phenotypic value and standard deviation are shown in Table 1. The data of growth traits, including birth weight, weight at 9 months, 15 months, 18 months, and 24 months, and average daily gain (ADG) from 6 months to 24 months, and carcass traits, including cold weight (CWT), backfat thickness (BF), *Longissimus dorsi* muscle area (LMA) and marbling score (MS), were measured. Hanwoo genomic DNA samples were obtained from 415 steers produced from 25 grand-sires half-sibs families. Genomic DNA from white blood cells was extracted by the phenol-chloroform method (Sambrook and Russell, 2001).

### DNA sequencing

We sequenced ECIP-1 (GeneBank accession no. AF061522), 31465_446 (GeneBank accession no. BV445837) and 12273_165 (GeneBank accession no. BV105733), including four SNPs (AH1_11, AH1_9, 31465_446, 12273_165) to identify the variation of the four SNP in 16 unrelated Hanwoo individuals using the BigDye Terminator (Ver 3.1) cycle sequencing kit (Applied Biosystems, Foster City, CA). Four primer sets for the amplification and sequencing analysis were designed on the basis of the GenBank sequence using the Primer3 software (http://frodo.wi.mit.edu/cgi_bin/primer3/primer3_www.cgi). The primer sequences used were as follows: AH1_11F, AH1_9F (5′-CCCGAAGCTCCCATGGTTAAG-3′) and AH1_11R, AH1_9R (5′-CCCTGGAAACCAGCCATTC

**Table 2.** BLAST and the genotype frequency of the 31465_446 and the 12273_165 SNP in 16 unrelated Korean cattle

| SNP | Genotype | Genotype frequency | Allele frequency | Heterozygosity | HWE[1] | BLAST |
|---|---|---|---|---|---|---|
| 31465_446 | CC(C) | 0.313 | 0.594 | 0.482 | 0.507 | Hatl3 |
| | CT | 0.563 | | | | |
| | TT(T) | 0.125 | 0.406 | | | |
| 12273_165 | AA(A) | 0.063 | 0.251 | 0.375 | 0.957 | LOC534614 |
| | AG | 0.375 | | | | |
| | GG(G) | 0.563 | 0.751 | | | |

[1] p value for deviation of genotype distribution from Hardy_Weinberg equilibrium (HWE).

TC-3′) for ECIP_1, 31465_446F (5′-AAGCTGGGGAGAT GAGTGTG-3′) and 31465_446R (5′-AGCCATCAATAGG GGATTGG-3′) for STS (GeneBank accession no. BV445837), 12273_165F (5′-TGGAAGTTGCTCTTGATA AGGTG-3′) and 12273_165R (5′-TCCAGAGTTTGCA GGTGACA-3′) for STS (GeneBank accession no. BV105733). Sequence editing for the consensus contig formation was generated by visual confirmation, using the Sequencher 4.6 program (Gene Codes Corp., Ann Arbor, MI).

**Genotyping by single-base extension (SBE) and electrophoresis**

For the genotyping of polymorphic sites, amplifying and extension primers were designed for single-base extension (SBE) (Vreeland et al., 2002). The primer extension reactions were conducted with the SNaPshot ddNTP Primer Extension Kit (Applied Biosystems, Foster City, CA). In order to clean up the primer extension reaction, one unit of SAP (shrimp alkaline phosphatase) was added to the reaction mixture, and the mixture was incubated for 1 h at 37°C, followed by 15 min at 72°C for enzyme inactivation. The DNA samples, containing extension products, and Genescan 120 Liz size standard solution was added to HiDi formamide (Applied Biosystems, Foster City, CA) in accordance with the manufacturer's recommendations. The mixture was incubated for 5 min at 95°C, followed by 5 min on ice, after which electrophoresis was conducted using the ABI Prism 3100 Genetic Analyzer. The results were analyzed using the ABI Prism GeneScan and Genotyper software (Applied Biosystems, Foster City, CA).

For the genotyping of the polymorphic site for 12273_165 SNP, extension primers were designed for the single-base extension method (Vreeland et al., 2002). The probe sequence was 5′-TCAAATTGGATTGTGTCCCA-3′.

**Statistical analysis**

In order to evaluate the association between the four SNP and growth and carcass traits in the Hanwoo, sequence editing of the STS sequence containing four SNPs (AH1_11, AH1_9, 31465_446, 12273_165) was conducted with the Sequencher v4.6 program (Gene Codes Corp., Ann Arbor, MI), and only the two polymorphic SNPs (12273_165 and 31465_446 SNP) were identified.

The $x^2$ tests of genotype frequency were used to determine whether individual variants were in equilibrium at each locus in the population (Hardy-Weinberg equilibrium).

The phenotypic data for growth and carcass traits in the 415 animals were analyzed by the mixed ANCOVA (analysis of covariance) linear model using the PROC GLM module in SAS v9.1 (SAS Inst., Inc., Cary, NC). The following model was used : $Y_{ijklm} = \mu+YS_i+P_j+M_k+GS_m+\beta_{age}+e_{ijklm}$ in which $Y_{ijklm}$ is the phenotypic observations of the traits, $\mu$ is the overall mean of each trait, $YS_i$ is the fixed effect of year and calving season, $P_j$ is the fixed effect of the jth place at the calving, $M_k$ is the fixed effect of the SNP genotypes, $GS_m$ is the random effect of grand-sire, $\beta_{age}$ is the covariate for the age in days at slaughter, and $e_{ijkl}$ is the random error.

Additive effects were estimated by the difference between the average effect of two homozygous genotypes, and the dominance effects were estimated by subtracting the average of solutions for homozygous genotypes from that for the heterozygous genotypes (Chung et al., 2005).

## RESULTS

Previous studies have identified 11 QTL for average daily gain, backfat thickness, *Longissimus dorsi* muscle area and marbling scores in Korean cattle (Kim et al., 2003). We confirmed that the ILSTS035 microsatellite was located at a similar position to the four SNP (AH1_11, AH1_9, 31465_446 and 12273_165) on the EST-based SNP linkage map, including the microsatellite described by Snelling et al. (2005), and was mapped at the chromosome location of 88.329cM (Figure 1). The allele and genotype frequencies of the two SNPs in 16 unrelated individuals are shown in Table 2. The genotype frequencies (%) of 31465_446 SNP were 31.3, 56.3 and 12.5 for CC, CT, and TT, respectively, and those of 12273_165 SNP were 6.3, 37.5 and 56.3 for GG, GA and AA, respectively. Also, the allele frequencies for the C and T of 31465_446 SNP were 0.594 and 0.406, respectively. At the 12273_165 SNP polymorphism, the A allele frequency was 0.251 and G allele frequency was 0.751. The genotypic frequencies were in Hardy-Weinberg

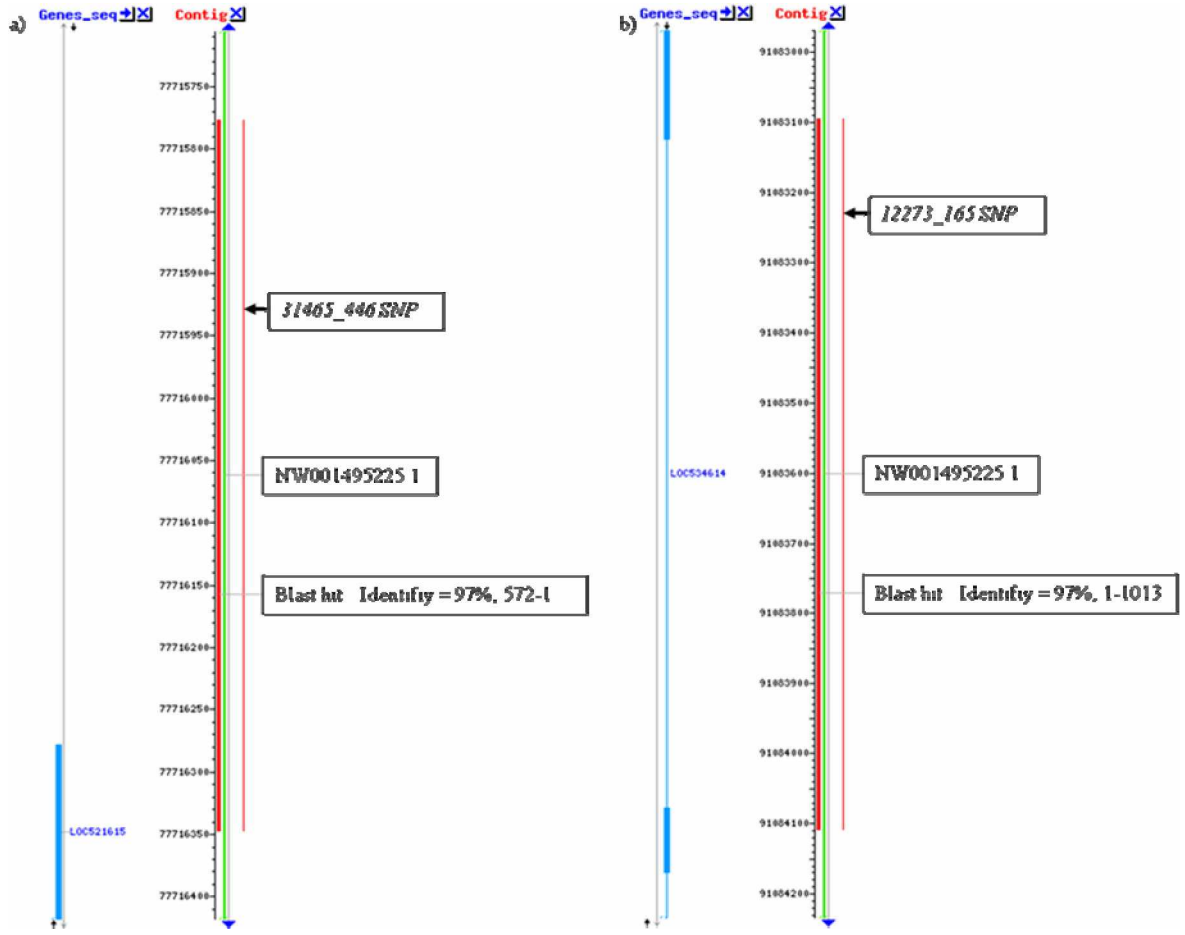


**Figure 2.** Alignment of the 31465_446and 12273_165 SNP position on BTA6 with the gene sequence map and contig map (*Bos Taurus* NCBI Map viewer, build 3.1).

equilibrium for the 12273_165 and 31465_446 SNPs, as determined by the Chi-square test ($p>0.05$).

As a result of our BLAST search at the NCBI web site, the sequences, including 31465_446 and 12273_165 SNP were similar to Hatl3 and LOC534614. Figure 2 showed the position of the 31465_446 and 12273_165 SNP in Hatl3 and LOC534614. Although the portion of the STS sequence (GeneBank accession no. BV445837) containing 31465_446 SNP overlapped with the Hatl3 gene, this SNP was not located proximal to or at the Hatl3 gene (Figure 2a). Instead, the 12273_165 SNP was located in an intron region of the unknown LOC534614 gene (Figure 2b). Thus, associations between the 12273_165 SNP in the LOC534614 gene and growth and carcass traits in Korean cattle (n = 416) were subsequently examined. By a BLASTX search at the NCBI web site using the mRNA sequence of LOC534614, this gene represented a protein similar to myosin heavy chain, fast skeletal muscle, embryonic isoform 1 in the dog and myosin_1 (Myosin heavy chain D) (MHC D) in *Macaca mulatta*. In cattle, the possibility that the myosin heavy chain gene was associated with muscle development was initially suggested by Martyn et al. (2004). Previous reports suggested that a variation in the non-coding region of the gene may play a significant function in the regulation of the expression level of a gene or in the definition of its tissue-specific expression pattern (Pagani et al., 2004; Weikard et al., 2005). This suggests that 12273_165 SNP in LOC534614 may be a candidate marker for meat quantity in Hanwoo.

The results of the least square mean for genotype, additive genetic effect and dominance genetic effect, and the association between the 12273_165 SNP and growth and carcass traits are shown in Table 3 and 4, respectively. The 12273_165 SNP had a significant effect on birth weight, the weight at 24 months (WT24) and average daily gain (ADG) ($p<0.05$), especially with regard to the additive genetic effect ($p<0.05$). But birth weight was not significant. Animals with the "AA" genotype had values 28.5 kg and 50 g lower in WT24 and ADG, respectively, than animals with the "GG" and "GA" genotypes. For carcass cold weight (CWT) and *longissimus dorsi* muscle area (LMA), a significant additive effect of the "GG" genotype over the "AA" genotype was observed (Table 4), but had no significant effect on LMA. Animals with the "AA"

**Table 3.** Levels of significance and least squares means for the effect of the 12273_165 SNP on growth traits, and estimates of additive and dominance effects in Korean cattle (n = 415)

| Growth traits[2] (kg) | p value | Genotype | | | Additive effect[3] | Dominance effect[4] |
|---|---|---|---|---|---|---|
| | | GG (266)[1] LSmean±SE | AG (126) LSmean±SE | AA (23) LSmean±SE | | |
| BW | 0.037 | 25.33±0.14 | 24.90±0.17 | 25.29±0.35 | -0.27±0.32 | 0.32±0.22 |
| WT9 | 0.282 | 223.17±1.91 | 219.81±2.49 | 217.62±5.90 | -5.55±6.17 | 0.58±3.92 |
| WT15 | 0.337 | 346.46±2.41 | 343.40±3.16 | 337.93±7.48 | -8.53±7.82 | -1.20±4.97 |
| WT18 | 0.232 | 417.87±2.76 | 412.06±3.62 | 409.99±8.57 | -7.88±8.96 | 1.87±5.69 |
| WT24 | 0.022 | 572.66±3.29[a] | 563.56±4.55[ab] | 544.09±11.02[b] | -28.51±11.94* | -3.69±7.23 |
| ADG | 0.050 | 0.76±0.01[a] | 0.75±0.01[a] | 0.71±0.02[b] | -0.05±0.02* | -0.02±0.01 |

[1] Figures in parenthesis refer to number of animals.
[2] BW = Birth weight. WT9 = Weight at 9 months. WT15 = Weight at 15 months. WT18 = Weight at 18 months. WT24 = Weight at 24 months. ADG = Average daily gain.
[3] Estimated by subtracting the solution for the "AA" genotype from that for the "GG" genotype.
[4] Estimated by subtracting the average of solutions for homozygous genotypes from that for heterozygous genotype.
[a,b] Mean with different superscripts within same column are significantly different ($p<0.05$).
* Effect was significant at $p<0.05$.

genotype had evidence of lower values in CWT and LMA than those of the "GA" and "GG" genotype. Animals with the "GG" genotype had the highest CWT and LMA (CWT = 319.74±2.04 and LMA = 75.74±0.65), when compared to the "AA" genotype (CWT = 299.28±6.88 and LMA = 71.82±1.70). However, we noted no statistical significance of the dominance effect of 12273_165 SNP for all the growth and carcass traits ($p>0.05$).

## DISCUSSION

Growth traits are economically relevant in the Hanwoo industry. Casas et al. (2000) reported that a significant QTL for growth traits was identified on BTA6 from the Belgian Blue×MARC III and Piedmontese×Angus population, and Casas et al. (2003) reported that a suggestive QTL was detected on the same chromosome for the *longissimus dorsi* muscle area and hot carcass weight in the *Bos indicus*×*Bos taurus* population. Also, a significant QTL was identified for birth weight and preweaning average daily gain in *Bos taurus* (Kneeland et al., 2004). In Hanwoo, Kim et al. (2003) detected a significant QTL for ADG and LMA on chromosome 6. Thus, we hypothesized that genes for growth traits were associated with the QTL in BTA6. In this study, we verified that the ILSTS035 microsatellite located in the 11 QTL region was located at a similar position to four SNPs (AH1_11, AH1_9, 31465_446 and 12273_165) on the EST-based linkage map. Only the 31465_446 and 12273_165 SNP polymorphisms were identified. Although the portion of the STS sequence containing 31465_446 SNP overlapped with Hatl3, the 31465_446 SNP was not located in the Hatl3 gene and the 12273_165 SNP was located in the intron region of the LOC534614 gene. The LOC534614 gene represents a protein similar to myosin heavy chain, fast skeletal muscle, embryonic isoform 1 in the dog and myosin-1 (Myosin heavy chain D) (MHC D) in *Macaca mulatta*. Consequently, we proposed that the LOC534614 gene was similar to the myosin heavy chain of skeletal muscle.

Growth is associated with skeletal muscle mass. The principal determinants of skeletal muscle mass are the muscle fiber number and muscle fiber size. During development, these factors are controlled by a series of events, including myoblast proliferation, myotube

**Table 4.** Levels of significance and least squares means for the effect of the 12273_165 SNP on carcass traits and the estimates of additive effect and dominance effect in Korean cattle (n = 415)

| Carcass traits[2] | Significance p value | Genotype | | | Addtive effect[3] | Dominance effect[4] |
|---|---|---|---|---|---|---|
| | | GG (266)[1] LSmean±SE | AG (126) LSmean±SE | AA (23) LSmean±SE | | |
| CWT | 0.008 | 319.74±2.04[a] | 313.53±2.84[ab] | 299.28±6.88[b] | -15.58±6.66* | -3.56±4.23 |
| BF | 0.115 | 7.47±0.22 | 6.26±0.58 | 6.26±0.58 | -0.97±0.57 | -0.49±0.38 |
| LMA | 0.084 | 75.74±0.65[a] | 75.11±0.78[a] | 71.82±1.70[b] | -4.03±1.59* | -1.93±1.06 |
| MS | 0.473 | 5.49±0.31 | 5.73±0.36 | 4.77±0.80 | -0.50±0.74 | -0.76±0.49 |

[1] Figures in parenthesis refer to number of animals.
[2] CWT = Carcass cold weight. BF = Backfat thickness. LMA = *Longissimus dorsi* muscle area. MS = Marbling score.
[3] Estimated by subtracting the solution for the "GG" genotype from that for the "AA" genotype.
[4] Estimated by subtracting the average of solutions for homozygous genotypes from that for heterozygous genotype.
[a,b] Mean with different superscripts within same column are significantly different ($p<0.05$).
* Effect was significant at $p<0.05$.

formation, and myofiber maturation. A number of regulatory factors can influence each of these stages of muscle development, including the genetic background of animals in a breed. In normal bovine muscle, fiber size varies according to fiber type. Type 2B fibers have the largest cross-sectional area, type 2A fibers are intermediate and type 1 fibers are the smallest. Therefore, the sequence of MHC isoform variation is an important determinant of skeletal muscle fiber type and there are developmental differences in MHC expression between normal-muscle and double-muscle cattle. Myostatin is a negative regulator of muscle mass (McPherron et al., 1997), which has been shown to inhibit both myoblast proliferation (Joulia et al., 2003) and differentiation (Rios et al., 2003). Previous studies have generally shown a positive association between myostatin expression and fast MHC isoforms. These results show that later muscle development in DM (double-muscle) fetuses is delayed relative to NM (normal-muscle) with regard to the expression of MHC (Myosin heavy chain) isoforms (Martyn et al., 2004).

By statistical analysis, the 12273_165 SNP showed evidence of a significant association with growth traits (Tables 3 and 4). The 12273_165 SNP was located at the intron region closed to exon16 in the LOC534614 gene.

Although the majority of the SNP that showed associations with phenotypes do not induce amino acid changes, these SNP may be linked to detect causative mutation or nearby QTL. As more knowledge is available on the manner in which noncoding sequences influence gene function, the manner in which these SNP contribute to variation in these economic traits may eventually become apparent. It is also possible that they are linked to other causative mutations that have not yet been detected (Sherman et al., 2008). It remains unclear as to the manner in which this mutation causes these effects, partly because the SNP is intronic and, therefore, does not appear to cause any amino acid changes to the LOC534614 protein.

In conclusion, the results of this study demonstrated that the 12273_165 SNP may represent a useful candidate for genetic improvement for growth, and suggested that the hypothetical gene may be associated with meat quantity in Hanwoo. Therefore, functional validation of polymorphisms in LOC534614 should be performed in the future.

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