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Association of bovine carcass phenotypes with genes in an adaptive thermogenesis pathway

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Abstract Associations of carcass phenotypes with genes regulating fat and energy metabolism involved in adaptive thermogenesis were examined in beef cattle. Carcass weight (CW) was found to be associated with MAP2K6 and UCP2 genes; back fat thickness (BFT) was found to be associated with PPARGC1A, MAP2K6, and UCP2 genes; marbling score (MS) was found to be associated with PPARGC1A and MAP2K6 genes; and eye-muscle area (EMA) was found to be associated only with UCP2 gene ($P < 0.05$). Further analyses found significant associations of interactions between PPARGC1A and MAP2K6 genes with CW and MS. Especially, interactive genetic associations were identified between c.424 and 222 G>A in PPARGC1A and c.17-10118 T>G in MAP2K6 and between c.228+28619 A>G in PPARGC1A and c.17-10118 T>G in MAP2K6, and they were both detected for CW and MS at a significant level ($P < 0.05$). The current study suggested that the individual and interactive associations of PPARGC1A, MAP2K6, and UCP2 genes with carcass phenotypes might be resulted from the pathway with fat and energy metabolism through the adaptive thermogenesis.

Keywords Carcass weight · Epistasis · Genetic association · Marbling score

Introduction

Associations of individual candidate genes with bovine phenotypes have been widely identified. For example, the gene encoding uncoupling protein (UCP) was associated with hot carcass weight and backfat thickness [1, 2], and the gene encoding peroxisome proliferator-activated receptor-γ coactivator-1α (PPARGC1A) was associated with milk production and its components [3, 4]. The two genes are involved in fat and energy metabolism and thus are good candidate genes in influencing carcass traits that have been a great interest to beef cattle geneticists. Even, they are both downstream genes of β-adrenergic receptor in an adaptive thermogenesis pathway [5]. Nevertheless, no attempt has been made to simultaneously examine associations of bovine carcass traits with such genes in a candidate pathway. In the current study, we investigated associations of single nucleotide polymorphisms (SNPs) in the candidate genes with carcass phenotypes of beef cattle and also identified interactive associations of the genes.

Materials and methods

Animals and phenotype

An indigenous beef cattle breed called Hanwoo in Korean or Bos taurus coreanae, has been maintained without

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introducing any other germplasm for 20 centuries since the crossbred of European *Bos primigenius* and Indian *Bos indicus* moved from China to Korea [6]. Since the Korean cattle have been used as draught animals until 1970s, their meat production has been unsatisfactory. Thus genetic improvement of the meat quantity and quality became one of the most important goals in the Korean animal industry [7]. A total of 380 Hanwoo steers from the Hongcheon Federation of Livestock Cooperation in Korea was used in the current study. They were assumed to be not closely related since each individual had different parents. They were born in 2005 and 2007 and slaughtered after average 871 days at the same slaughter house according to standard industrial procedures suggested by the Ministry for Food, Agriculture, Forestry, and Fisheries. Twenty four hours after chilling, the phenotypic data were measured. Each side of carcass was weighted and summed up as carcass weight (CW, kg), and CWs were preliminary adjusted for age at slaughter using a linear regression. Back fat thickness (BFT, mm), eye muscle area (EMA, cm^2), and marbling score (MS) were measured or scored in the left carcass cut across the vertebra between the last thoracic vertebra and the first lumbar vertebra. The MS was scored from 1 to 9 with the mean of 6.8 where a larger score meant more abundant intramuscular fat (Table 1, Supplementary figure 1).

Table 1 Average carcass phenotypes of Korean cattle used in the current study

Trait	Mean	SD	CV	Min.	Max.
CW (kg)	450.7	43.0	9.6	360	538
BFT (mm)	12.6	4.0	31.7	5	29
MS[a]	6.8	1.4	20.3	2	9
EMA (cm^2)	94.2	9.5	10.0	75	123

[a] The score was ranged from 1 (trace) to 9 (very abundant)

CW carcass weight, *BFT* back fat thickness, *MS* marbling score, *EMA* eye muscle area, *SD* standard deviation, *CV* coefficient of variation

Genotype

We selected bovine genes belonged to energy metabolism pathway from MAP3K4 to UCP. A total of 6 genes was analyzed in this study, and they were UCP1, UCP2, PPARGC1A, p38 MAPK, MAP2K6, and MAP3K4. One hundred SNPs were randomly selected among SNPs within the 6 bovine genes using the Livestock Genomics database (http://www.livestockgenomics.csiro.au/cow/). After excluding the SNPs located within spanning 1 kb from any other SNP, 72 out of 100 SNPs were remained. Twenty out of 380 steers were genotyped as a preliminary step to decide which SNPs were to be genotyped for the 380 steers. Among the 72 SNPs, 10 SNPs with their minor allele frequencies larger than 0.2 were included in this study. The 10 SNPs were not deviated from Hardy-Weinberg equilibrium ($P > 0.05$, Table 2), and thus their associations with carcass traits were examined.

Genomic DNA was extracted from tissue samples using a QIAamp Tissue Kit (Qiagen, Hilden, Germany). The SNPs of the 6 bovine genes were genotyped using the TaqMan polymerase chain reaction assay (Applied Biosystems, Foster City, CA). Reactions were carried out

Table 2 Single nucleotide polymorphisms (SNPs) analyzed in current study

SNP	BTA[a]	Position[b]	Gene	Gene region	Polymorphism	MAF[c]	HWE[d]
ss61493552	9	100553557	MAP3K4	Intron 1	c.6-7342 G>A	0.30	0.11
ss117965328	19	63038349	MAP2K6	Intron 11	c.928-287 G>A	0.17	1.00
rs41933161	19	63082777	MAP2K6	Intron 1	c.17-10118 T>G	0.24	0.54
ss86295156	19	63113627	MAP2K6	Intron 1	c.16+31296 T>C	0.47	0.31
ss86337580	19	63136938	MAP2K6	Intron 1	c.16+7985 A>G	0.28	1.00
ss86335517	23	10263128	P38 MAPK	Intron 1	c.116+5886 G>A	0.47	0.17
ss117968703	6	44772185	PPARGC1A	Intron 3	c.424-222 G>A	0.43	0.82
ss117968186	6	44804409	PPARGC1A	Intron 2	c.228+28619 A>G	0.45	0.57
ss86298148	17	18323055	UCP1	Exon 2	c.228 T>C	0.19	0.05
rs41255549	15	52967148	UCP2	Exon 3	c.81 T>G	0.41	1.00

[a] *BTA Bos taurus* autosome

[b] Base pair in chromosome

[c] *MAF* minor allele frequency

[d] *P*-value for testing Hardy-Weinberg equilibrium (HWE)

MAP3K4, mitogen-activated protein kinase kinase kinase 4, *MAP2K6*, mitogen-activated protein kinase kinase 6, *P38MAPK* p38 mitogen-activated protein kinase, *PPARGC1A* peroxisome proliferator-activated receptor-γ coactivator 1α, *UCP1* uncoupling protein 1, *UCP2* uncoupling protein 2

following the manufacturer's protocol. The reaction products were analyzed using ABI PRISM 7900HT (Applied Biosystems, Foster City, CA).

Statistical analysis

Single-locus genetic associations with carcass phenotypes were analyzed with following genotypic model.

$$Y_{ijkl} = \mu + sy_i + ss_j + g_k + e_{ijkl}$$

where Y_{ijkl} is carcass phenotype for slaughter year i, slaughter season j, genotype k, and animal l, μ is overall mean, sy_i is fixed effect for slaughter year i, ss_j is fixed effect for slaughter season j, g_k is fixed effect for genotype k ($k = 1$, 2, or 3), and e_{ijkl} is residual. Modified genotype effect was also applied by assuming dominance or recessive model.

Two-locus pairwise interactive genetic associations were analyzed with following genotype-based epistatic model.

$$Y_{ijklm} = \mu + sy_i + ss_j + g_k + g_l + i_{kl} + e_{ijklm}$$

where Y_{ijklm} is carcass phenotype for slaughter year i, slaughter season j, genotype k for locus *1*, genotype l for locus 2, and animal m, μ is overall mean, sy_i is fixed effect for slaughter year i, ss_j is fixed effect for slaughter season j, g_k is fixed effect for genotype k ($k = 1$, 2, or 3), g_l is fixed effect for genotype l ($l = 1$, 2, or 3), i_{kl} is fixed effect for interaction between genotype k and genotype l, and e_{ijklm} is residual. All the statistical tests were conducted using SPSS, release 12.0 (SPSS Inc., Chicago, IL), and their significances were determined with $\alpha < 0.05$.

Results

Five SNPs in MAP2K6, PPARGC1A and UCP2 were found to be significantly associated with the carcass phenotypes ($P < 0.05$, Table 3), and Tukey post-hoc tests showed differences among some genotypic groups ($P < 0.05$, Supplementary Table 1). Especially, all the 2 SNPs in MAP2K6 were found to be associated with MS, and all the 2 SNPs in PPARGC1A were found to be associated with both BFT. Most of SNPs were identified in dominance model except for the MAP2K6 c.928-287 G>A, which was identified in recessive model regardless of the phenotypes.

Further genetic association analyses found significant associations of interactions between genes with the carcass phenotypes ($P < 0.05$, Table 4), and Tukey post-hoc tests showed differences among some genotypic groups ($P < 0.05$, Supplementary Tables 2, 3, and 4). Interactions were found mostly between genes rather than within genes,

Table 3 Association of individual single nucleotide polymorphisms (SNPs) with carcass phenotypes in Korean cattle

Trait	Gene	SNP	ALLE		GENO		ADDE		DOME		REC		DOM		FG
			t	*P*-value	*F*	*P*-value	*t*	*P*-value	*t*	*P*-value	*t*	*P*-value	*t*	*P*-value	
CW	MAP2K6	c.928-287 G>A	−0.73	4.64×10^{-1}	**4.52**	$\mathbf{1.09 \times 10^{-2}}$	1.88	6.17×10^{-2}	**−2.91**	$\mathbf{3.84 \times 10^{-3}}$	**2.09**	$\mathbf{3.72 \times 10^{-2}}$	−1.55	1.22×10^{-1}	AA
	UCP2	c.81 T>G	**2.59**	$\mathbf{9.94 \times 10^{-3}}$	**3.74**	$\mathbf{2.37 \times 10^{-2}}$	**2.31**	$\mathbf{2.16 \times 10^{-2}}$	0.87	3.84×10^{-1}	1.41	1.59×10^{-1}	**2.68**	$\mathbf{7.83 \times 10^{-3}}$	GG
BFT	MAP2K6	c.17-10118 T>G	−1.70	8.98×10^{-2}	2.24	1.10×10^{-1}	−0.57	5.68×10^{-1}	−1.23	2.21×10^{-1}	−0.17	8.69×10^{-1}	**−2.04**	$\mathbf{4.18 \times 10^{-2}}$	GG
	PPARGC1A	c.424-222 G>A	**−2.15**	$\mathbf{3.26 \times 10^{-2}}$	**5.02**	$\mathbf{6.60 \times 10^{-3}}$	−1.69	9.13×10^{-2}	**−2.32**	$\mathbf{2.12 \times 10^{-2}}$	−0.24	8.13×10^{-1}	**−3.06**	$\mathbf{2.44 \times 10^{-3}}$	AA
	PPARGC1A	c.228+28619 A>G	−1.85	6.57×10^{-2}	**4.54**	$\mathbf{1.07 \times 10^{-2}}$	−1.55	1.23×10^{-1}	**−2.37**	$\mathbf{1.84 \times 10^{-2}}$	-0.05	9.61×10^{-1}	**−2.84**	$\mathbf{4.77 \times 10^{-3}}$	GG
	UCP2	c.81 T>G	**3.66**	$\mathbf{3.00 \times 10^{-4}}$	**6.79**	$\mathbf{1.12 \times 10^{-3}}$	**3.43**	$\mathbf{6.88 \times 10^{-4}}$	0.49	6.23×10^{-1}	**2.45**	$\mathbf{1.47 \times 10^{-2}}$	**3.39**	$\mathbf{8.04 \times 10^{-4}}$	TT
MS	MAP2K6	c.928-287 G>A	1.26	2.09×10^{-1}	2.69	6.76×10^{-2}	**2.32**	$\mathbf{2.13 \times 10^{-2}}$	−1.95	5.25×10^{-2}	**2.32**	$\mathbf{2.08 \times 10^{-2}}$	0.63	5.28×10^{-1}	AA
	MAP2K6	c.17-10118 T>G	−0.96	3.39×10^{-1}	**3.07**	$\mathbf{4.67 \times 10^{-2}}$	0.61	5.09×10^{-1}	**−2.28**	$\mathbf{2.33 \times 10^{-2}}$	1.11	2.69×10^{-1}	−1.75	8.07×10^{-2}	GG
	PPARGC1A	c.228+28619 A>G	−1.62	1.07×10^{-1}	2.34	9.68×10^{-2}	−1.42	1.55×10^{-1}	−1.43	1.53×10^{-1}	−0.42	6.75×10^{-1}	**−2.14**	$\mathbf{3.34 \times 10^{-2}}$	AA
EMA	UCP2	c.81 T>G	**−2.04**	$\mathbf{4.22 \times 10^{-2}}$	2.42	8.87×10^{-2}	**−2.18**	$\mathbf{3.01 \times 10^{-2}}$	0.83	4.08×10^{-1}	**−2.10**	$\mathbf{3.69 \times 10^{-2}}$	−1.33	1.86×10^{-1}	TT

SNPs significantly associated by *F*- or *t*-statistic are presented ($P < 0.05$). Statistics with $P < 0.05$ are shown in ***bold***

MAP2K6 mitogen-activated protein kinase kinase 6, *PPARGC1A* peroxisome proliferator-activated receptor-γ coactivator 1α, *UCP2* uncoupling protein 2, *CW* carcass weight, *BFT* back fat thickness, *MS* marbling score, *EMA* eye-muscle area, *ALLE* allelic model, *GENO* 2-df genotypic model, *ADDE* additive effect, *DOME* dominance effet, *REC* recessive model to test for minor allele, *DOM* dominance model to test for minor allele. *FG* favorable genotype suggested for animal breeding

Table 4 Interactive association of paired single nucleotide polymorphisms (SNPs) with carcass phenotypes in Korean cattle

Trait	SNP 1	SNP 2	χ^2	*P*-value	FCG
BFT	PPARGC1A c.424-222 G>A	PPARGC1A c.228+28619 A>G	6.442	1.1×10^{-2}	AA^1AG^2,GA^1AA^2
CW	PPARGC1A c.424-222 G>A	MAP2K6 c.17-10118 T>G	7.717	5.5×10^{-3}	AA^1GG^2,GG^1TT^2
	PPARGC1A c.228+28619 A>G	MAP2K6 c.17-10118 T>G	7.512	6.1×10^{-3}	GG^1GG^2,AA^1TT^2
MS	PPARGC1A c.424-222 G>A	MAP2K6 c.17-10118 T>G	6.359	1.1×10^{-2}	GG^1TT^2
	PPARGC1A c.228+28619 A>G	MAP2K6 c.17-10118 T>G	5.485	1.9×10^{-2}	GG^1GG^2,AA^1TT^2

PPARGC1A peroxisome proliferator-activated receptor-γ coactivator 1α, *MAP2K6* mitogen-activated protein kinase kinase 6, *BFT* back fat thickness, *CW* carcass weight, *MS* marbling score, *FCG* favorable combined genotypes. FCGs were selected based on marginal and interactive effects of SNP pairs, and their *superscripts* indicate SNPs

indicating epistasis (Table 4). Most of the epistatic effects were discovered between PPARGC1A and MAP2K6 genes. Especially, the interaction between c.17-10118 T>G in MAP2K6 and c.424-222 G>A in PPARGC1A and the interaction between c.17-10118 T>G in MAP2K6 and c.228+28619 A>G in PPARGC1A were observed for CW as well as for MS. These 3 SNPs in MAP2K6 and in PPARGC1A genes were found to be interactively associated with CW in spite of no individual associations.

Discussion

We examined genetic associations of bovine carcass phenotypes with genes included in a pathway of fat and energy metabolism of adipogenesis [8], mitochondrial biogenesis [9], and uncoupling respiration [10]. In the current study, 5 SNPs within MAP2K6, PPARGC1A, and UCP2 genes in the pathway were found to be associated with carcass phenotypes.

The associations of UCP2 gene with CW, BFT, and EMA might be resulted from adaptive thermogenesis in skeletal muscles and brown adipose tissues by uncoupling oxidative phosphorylation of UCPs [10]. Especially, the associations with UCP2 gene but not with UCP1 could be further explained by their tissue-specific expression. The UCP2 has been found to be expressed in a variety of tissues such as skeletal muscle and brown adipose tissue [10] while UCP1 has been found to be expressed exclusively in brown adipose tissue [11]. Since large animals do not have any definite brown adipose tissue [12], UCP2 would induce adaptive thermogenesis largely in skeletal muscle of cattle. The function might lead to the association of UCP2 in the current study. This was consistent with previous studies where UCP2 gene was found to be associated with intramuscular fat accumulation, backfat, and body weight of cattle [1, 13].

Since mitochondrion mediates energy expenditure by converting foods to carbon dioxide, water, and adenosine triphosphate, an increase of mitochondria through PPARGC1A must be also stressed for adaptive thermogenesis. PPARGC1A stimulated mitochondrial biogenesis in muscle cells by regulating nuclear respiratory factors [9, 14]. Expression of PPARGC1A increased with high mitochondrial density [15]. Furthermore, PPARGC1A regulated the expression of UCP2 directly as well as through PPARγ in muscles [12, 16]. The functions of PPARGC1A on energy expenditure supported its association with BFT and MS.

The genetic association of MAP2K6 with carcass traits might be demonstrated by fat accumulation through adipogenesis. This was because the MAP2K6 would activate p38 MAPK, which could promote adipogenesis [8] through regulation of PPARγ and CEBPβ [17, 18].

The current study revealed associations of multiple genes with a specific carcass phenotype. Mainly, all the MAP2K6, PPARGC1A, and UCP2 genes influenced BFT. Since the genes played a vital role in energy and fat metabolism in the same pathway [19], their interactive associations were speculated. The current pairwise association analysis showed that more variability of carcass phenotypes was explained by the interplay between genes. Epistatic effects between PPARGC1A and MAP2K6 genes were observed for CW and MS. Especially interactive associations were identified by the same two pairs of SNPs. One was c.424-222 G>A in PPARGC1A and c.17-10118 T>G in MAP2K6, and the other was c.228+28619 A>G in PPARGC1A and c.17-10118 T>G in MAP2K6. The interactive effect between c.424-222 G>A and c.17-10118 T>G was corresponding to that between c.228+28619

A>G and c.17-10118 T>G for both CW and MS. This might be caused by a strong linkage disequilibrium ($R^2 = 0.855$, $D' = 0.965$) of the two SNPs in PPARGC1A. The findings of interactions also supported an important role of the pathway in carcass phenotypes.

In summary, the associations of 5 SNPs in PPARGC1A, MAP2K6, and UCP2 with carcass phenotypes identified in the current study might be attributed to the mechanisms of uncoupling respiration, mitochondrial biogenesis, and adipogenesis in a pathway. Incorporating their individual and interactive effects into breeding programs of beef cattle is suggested to improve quality and quantity of the Korean beef.

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