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Assessment of genetic diversity and Signatures of Selection in Korean Cattle Populations

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Abstract

Based on coat color phenotypes, Korean native cattle are categorized into four breeds/strains (Brown Hanwoo, Black Hanwoo, and Brindle Hanwoo) and each strain has experienced different demographic events. In this study, to decipher the patterns of genetic diversity and identify signatures of selection, we genotyped 284 animals representing 3 Korean cattle breeds using the 600K Affymetrix chip. The lowest within-breed genetic diversity was found for Brindle Hanwoo (Chikso) and Black Hanwoo (Heugu) cattle, probably a result of a reduction in effective population size. Our principal component and phylogenetic analyses revealed a marked clustering of the three cattle breeds according to their phenotypic /coat color basic discriminations. The mean estimates of r^2 were 0.30, 0.29 and 0.29 in the Chikso, Heugu, and Hanwoo cattle, respectively. The Chikso and Heugu breeds reliably showed smaller N_e across generations. Our signatures of divergence selection analyses identified functionally important genes. Notably, some of the candidate genes have previously been known to affect growth, body size and stature (*GLI3, XKR4, CDK6, DIAPH3, ELF1, FTO*), meat quality (*XKR4, DECR1, FTO, DIAPH3*), fatty acid metabolism and composition (*ELF1, PPARD, MTTP*), and feed efficiency (*XKR4, NR1I2*). Gene Ontology(GO) analysis showed that that the candidate genes were associated with functional terms relevant to meat quality traits (fatty acid beta-oxidation, adipose tissue development) and pigmentation. The genetic diversity and structure of the three Korean cattle breeds can be explained by demographic events, remarkably genetic drift and selective breeding. It can be suggested that genes with known effect on growth and meat quality traits are potential candidates for further validation and inclusion in the beef selection program.

Keywords: Affymetrix chip, Chikso, Hanwoo cattle, linkage disequilibrium, candidate genes,

Introduction

The history of cattle production in the Korean Peninsula dates back to over 5000 years (Lee et *al.,* 2014; Payne and Hodges, 1997). Analysis using mtDNA showed that Korean cattle carry taurine haplotype (Mannen *et al.,* 2004). Concurrent with the mtDNA results, in our recent study, we traced little genetic influence of African and Asian indicine in Korean Hanwoo cattle (Edea *et al.,* 2015). On the other hand, SNPs based analysis did detect the genetic influence of African taurine and indicine in Hanwoo (Decker *et al.,* 2014), which was believed to be introgressed by European cattle via the Silk Road (Christian, 2000). In their microsatellite-based study of north-east Asian cattle, Kim *et al.* (2002) have shown that Korean cattle are much closer to Chinese cattle but distinct from Japanese Black cattle.

Based on coat color phenotypes and geographical distribution, Korean native cattle are categorized into four breeds/

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strains: Brown Hanwoo, Jeju Black, Heugu, and Brindle Hanwoo/Chikso (Lim *et al.,* 2016; Suh *et al.,* 2014). Of these the four breeds, the Brown Hanwoo is the predominant breed in terms of population size (3, 000,000) and geographical distribution, whereas the population sizes of Chikso and Heugu were estimated to be only between 300 to 400 heads (Suh *et al.,* 2014). Therefore, the later breeds may have faced severe population bottleneck. Assessment of the possible impacts of demographic events on the landscape of genetic diversity and population structure are of particular importance for the ongoing conservation program.

During the earlier periods, Korean cattle were majorly kept for the draft, transportation, and socio-cultural purposes (Lee *et al.,* 2014b). Driven by consumers demand for quality beef products, however, since the 1960s, cattle breeding objective has geared towards meat production (Lee *et al.,* 2014a; Park *et al.,* 2013a) and has resulted in a substantial genetic gain. Accordingly, the Brown Hanwoo cattle breed has been subjected to intensive selection for beef and meat quality traits (Lee *et al.,* 2014b; Park *et al.,* 2013). Following decades of selection, a substantial genetic gain has been achieved for carcass weight and eye muscle area (Park *et al.,* 2013b). For instance, an annual weight gain of 8 kg in carcass weight was reported (NIAS, 2009). Similarly, yearling weight was increased from 315.54 kg to 355.06 kg during the past 13 years (Park *et al,* 2013). On the other hand, the two native Korean cattle breeds have not been selected for beef traits. Due to selection against certain phenotypes (e.g. coat color), the Brindle (Chikso) and Black (Heugu) Korean cattle have received less attention, as a result, their population sizes have been dramatically declined. The intensive selection of Hanwoo cattle for beef traits may have left genomic signatures of selection within genes associated with beef traits. Genomic comparison of selected (Hanwoo) and unselected (Chikso and Heugu) cattle breeds can provide some insight into the possible impacts of human-guided selection in shaping the genetic composition of the former breed group. Furthermore, it can facilitate the identification of causal variants associated with a trait of interest. In this study, we present the genome-wide genetic diversity and signatures of selection analyses in three Korean native cattle breeds exposed to different demographic events/ selective pressures.

Materials and Methods

Cattle breeds, genotyping and quality control

In this study, we sampled three native Korean cattle populations, namely Brown Hanwoo (n = 248), Chikso (Brindle Hanwoo, n = 18) and Heugu (Black Hanwoo, n = 18). To account for the effect of sample size on estimates of genetic diversity and population structure analysis, we randomly selected 18 Hanwoo samples from 248 individuals. All individuals were genotyped with the 600K Affymetrix chip, which contains a total of 630,973 autosomal SNPs. The SNP markers were screened for a call rate < 95%, minor allele frequency (MAF) < 0.05. Following applying the above quality control criteria, 354,337 autosomal SNPs were retained and used for downstream analysis.

Data analyses

Genetic diversity was estimated for each breed using PLINK (Purcell et al. 2007). Inbreeding coefficient and animal relatedness were estimated as the proportion identity-by-decent (IBD) between sample pairs within the breed as a PI_HAT value using the same package. A principal component analysis (PCA) was also performed on 354,337 SNPs using SNP and Variation Suite v8.5.0 (Golden Helix, Inc., Bozeman, MT, www.goldenhelix.com). Linkage disequilibrium (LD) was estimated between adjacent SNPs. Inter-SNP distances were binned into different categories and estimates of r^2

were averaged for each inter-SNP distance category. Effective population size (*Ne*) in each breed was estimated from linkage disequilibrium using SNeP tool (Barbato et al. 2015) with the default settings.

Genetic differentiation (F_{ST}) was estimated with unbiased estimator according to (Weir & Cockerham 1984) using SNP and Variation Suite v8.5.0 (Golden Helix, Inc., Bozeman, MT, www.goldenhelix.com). Based on the results of PCA and neighbor-net tree, two pairwise comparisons (Hanwoo-Chikso, and Hanwoo- Heugu) were performed to identify genomic regions that may be under selection. The highly-differentiated regions representing the top 0.5% were used to define genomic regions under divergence selection. We further performed functional annotation analysis using the web-based DAVID Bioinformatics resources (v. 6.8, https://david.ncifcrf.gov/).

Results and discussion

Genetic diversity, population structure, and demographic history

Compared to the Brown Hanwoo cattle, the two Korean cattle breeds (Chikso and Heugu) display low levels of observed heterozygosity (Table 1). These values are higher than those (0.26-0.29) estimates by (Kim *et al.,* 2018), but far lower than the microsatellite-based values (0.67) (Suh *et al.,* 2014). The low level of genetic diversity for Chikso and Heugu is possibily attributed to genetic drift associated with low effective population size. The levels of inbreeding coefficients were found to be -0.094, -0.127 and -0.064 for Chikso, Heugu, and Hanwoo, respectively. The estimated average relatedness as measured by the proportion of IBD was the lowest for Hanwoo (0.055). The analysis of molecular variance revealed that 10.06% ($P < 0.000$) of the total variability can be attributed to among populations, and almost 90% of the variation was due to within populations.

Table 1. Indexes of genetic diversity and breed specific SNPs

Parameter	Hanwoo	Chikso	Heugu
H_O	0.36	0.32	0.32
H_E	0.35	0.29	0.29
f	-0.001	-0.094	-0.127
PI_HAT	0.168	0.168	0.245
Breed specific SNPs	15515	476	436
MAF Min	0.05	0.05	0.05
Max	0.41	0.42	0.42
Average	0.11	0.13	0.15

Breed-specific SNPs can be used for product traceability and breed discrimination/assignment (Negrini *et al.,* 2009). A SNP was breed-specific when it was segregating/ polymorphic (MAF > 0.05) in the one breed but fixed in the other breeds (Czech *et al.,* 2018). The highest number of breed-specific SNPs was found in Hanwoo and the lowest for the Chikso breed. Annotation of breed-specific SNPs showed that the SNPs were associated with 125 genes in Chikso and 116 in Heugu.

Principal components analyses nearly clustered the three breeds according to their phenotypic /coat color based discriminations. As well portrayed in Figure 1, the PC1 accounted for about 48.48% of the variation and separated Hanwoo and Chikso from the Korean Black cattle. The PC2 separated Brown Hanwoo from Brindle Hanwoo(Chikso).

Consistent with PCA results, our Neighbor-joining (NJ) confirms the PCA results (Figure 2). The Heugu breed was distantly separated from the two mainland cattle breeds, possibly due to genetic drift associated with small effective population size.

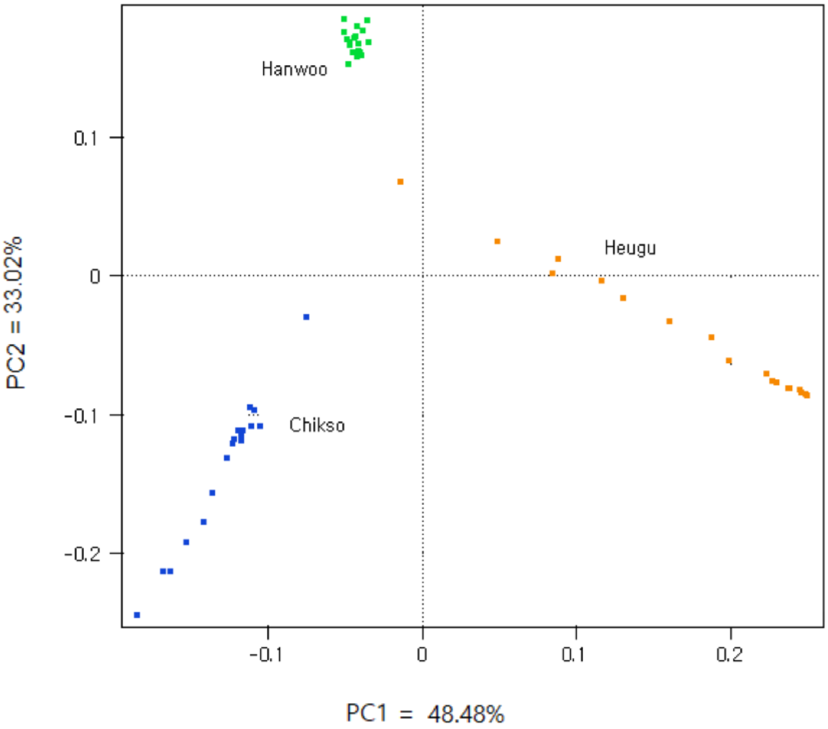

Figure 1. Individual animals clustering based on principal component analysis (PCA)

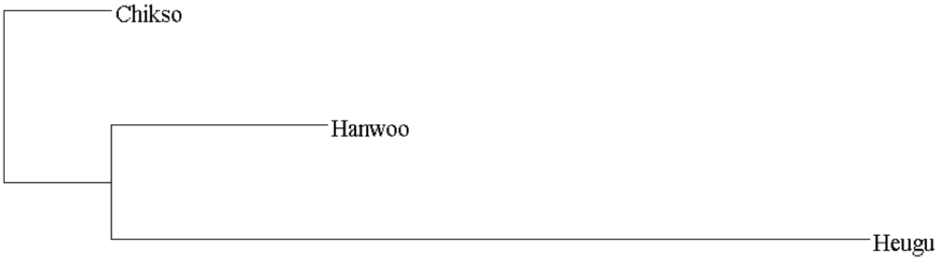

Figure 2. Genetic relationship among 3 Korean cattle breeds

LD and effective population size

The overall mean r^2 values were 0.29 ± 0.35, 0.29 ± 0.36 and 0.27 ± 0.30 in Chikso, Heugu, and Hanwoo, respectively. The value obtained in Hanwoo was higher the reported 0.17 and 0.23 using the 50K and 80K BeadChips, respectively (Edea *et al.,* 2015). The average LD values observed in this study here were higher than those reported for the Nellore cattle breed ($r^2 = 0.17$) (Espigolan *et al.*, 2013). For inter-SNP marker distances of 20–40 kb, average estimated LD (r^2) values for Chikso, Heugu, and Hanwoo were 0.23, 0.23 and 0.21, respectively (Figure 3). At shorter SNP distances (0-40 kb), Hanwoo had shown lower LD than the Chikso and Heugu cattle breeds. In the Hanwoo cattle, r^2 values dropped from 0.28 to 0.11 when the inter-marker distance increased from 1–10 to 300–700 kb (Figure 3). The higher LD at a shorter distance in the two Korean cattle breeds could be attributed to a reduction in their effective population sizes across generations. As expected, the two Korean cattle (Chikso and Heugu) displayed smaller N_e across generations (Figure 4). These smaller N_e values obtained for Chikso and Heugu breeds are in concurrent with the observed lower within-breed genetic diversity and higher LD at shorter distances. The N_e values obtained in this study for the last 13 generations are lower than those reported for three Korean cattle populations (Kim *et al.,* 2018). Estimates of N_e found in Hanwoo is higher than previously found for Jersey ($N_e = 82$), but lower than the value ($N_e = 153$) reported in Charolais (Edea *et al.,* 2018).

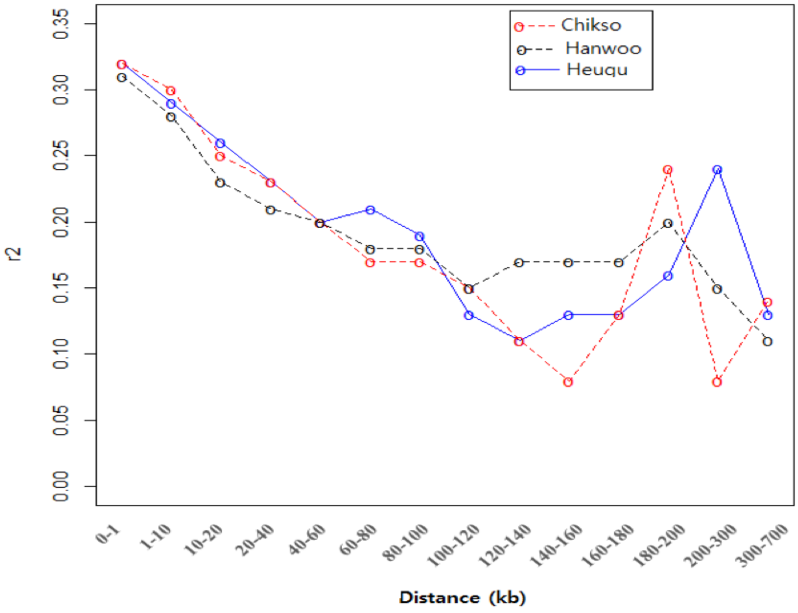

Figure 3. Linkage disequilibrium (r^2) decay in three Korean cattle breeds

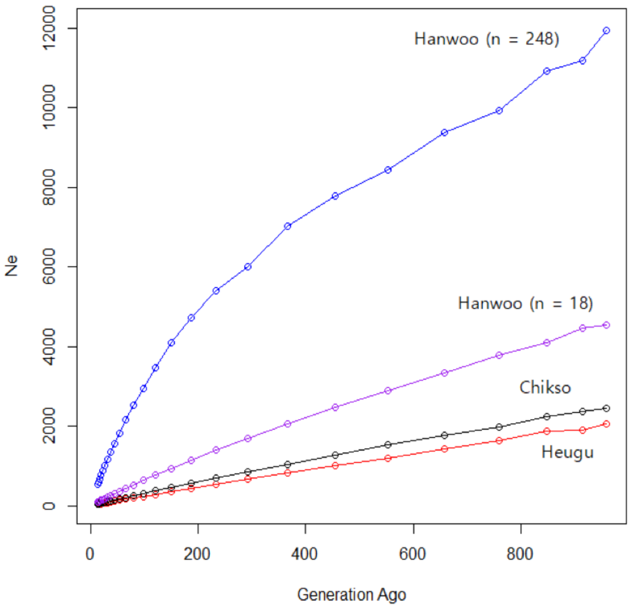

Figure 4. Effective population size across generations in three Korean cattle breeds

Candidate regions under selection

During their evolutionary histories, Korean cattle have exposed to different demographic events. The brown Hanwoo cattle have been under selection for beef traits since the 1960s, whereas the two Korean cattle breeds (Chikso and Heugu) have received less attention and are not the focus of systematic selection. The difference in demographic events and selective pressures are expected to shape the genomes of these population differently. In an attempt to capture the possible impacts of human-guided selection and/or genetic drift on the genomes of the Korean cattle breeds, we conducted a genome-wide comparative analysis on 284 animals representing three Korean cattle breeds using 354,337 SNPs. The mean genomic FST values ranged from 0.06 between Hanwoo an Heugu and to 0.13 between Chikso and Heugu, respectively. Overall, the top 0.5% FST values contained 409 and 419 genes in the Hanwoo/Chikso and Hanwoo/Heugu comparisons, respectively (Tables S1a and b). For the former breed pair comparison, the largest number of genes per chromosome were identified on BTA1, and BTA6 (31 genes). In Hanwoo-Chikso pair, the most strongly selected regions were detected on BTA6 (26.16 Mb), BTA7 (28.22 Mb), BTA8(91.27 M), and BTA17 (25.05, 35.67 Mb) containing 4 genes (*MAPKSP1, LOC100126815, LOC100336402, CTNND2,* respectively). For Heugu-Hanwoo pair, candidate genes associated with high FST value were noted on BTA7, 17, and 18. We further assessed selective signals between the two pairwise comparisons. Shared signals of selection were detected on BTA1 (62.17 Mb), BTA2 (34.25 Mb), BTA3(66.80-68.72 Mb), BTA5(51.27 Mb), BTA6(43.80; 60.20-60.30 Mb), BTA14 (48.57, 72.49 Mb), BTA17(25.05 Mb), BTA21 (59.41 Mb), BTA22 (37.65 Mb), BTA23(54.63 Mb), and BTA25 (38.20 Mb) containing *LOC538060, IFIH1, GIPC2, LOC782689, MON2, GBA3, KLB, C6H4orf34, EXT1, CDH17, LOC100336402, PPP4R4, ATXN7, LOC540231,* and *LOC615412* candidate genes.

The brown Hanwoo cattle breed has been phenotypically subjected to intensive selection for meat production and quality traits including carcass weight, eye muscle area, backfat thickness, and marbling score (Park *et al.,* 2013). Interestingly, we identified genes under selection and known to be associated with growth, stature, and carcass quality (Table 2). The *XKR4* gene has been reported to be associated with backfat thickness (Porto Neto *et al.,* 2012) feed intake and growth traits (Medeiros *et al.,* 2017; Lindholm-Perry et al., 2102). *MTTP* contains QTL for fatty acid composition (Corominas *et al.,* 2013) and associated with lipid metabolism in Hanwoo (Baik *et al.,* 2015). The remarkable effect of the *FTO* gene on live weight and carcass characteristics has been extensively investigated in many studies. In their association studies using Simmental and Brown cattle, Skok *et al.* (2015) demonstrated that variants of *FTO* gene were associated with lean meat percentage, fat percentage, and live weight at slaughter. Additionally, this gene has been investigated for its effect on body mass index in humans and growth and carcass traits in pigs and cattle (Rempel *et al.,* 2012; Fontanesi *et al.,* 2009; Frayling *et al.,* 2007).

Polymorphisms of the *GLI3* gene were associated with weight at birth and 6 months in Chinese cattle (Huang *et al.,* 2013), *ELF1* is involved in lipid metabolism (Jin *et al.,* 2009; Chang and Miyamoto, 2006) and regulates adipocyte differentiation (Baek and Baek, 20136). It has also been reported that *ELF1* regulates intramuscular fat in cattle (Ramayo-Caldas *et al.,* 2014; Rudra *et al.,* 2012). *DIAPH3* is associated with height variation (Metzger *et al.,* 2018) and also down-regulated in the longissimus dorsi muscle in Korean cattle (Lee *et al.,* 2017). Another potential candidate genes identified were *CDK6, SENP6,* and *DECR1*. SNP in the promoter region of the *CDK6* gene was found to be significantly associated with body length and heart girth in Chinese and Simmental cattle breeds (Liu *et al.,* 2001). *DECR1* is identified to be associated with ultrasound backfat in European beef breeds (Angus, Charolais) (Marques *et al.,* 2009), linked to lipid metabolism and linoleic content (Amills *et al.,* 2005), and contains QTL for fatty acid composition in pigs (Clop *et al.,*

Table 2. Candidate genes detected in the Chikso-Hanwoo analysis

Chr	Position	Candidate genes	Function
1	20721975	*USP25*	Meat quality
1	65226899	*NR1I2*	Feed efficiency
1	81995813	*TRA2B*	Growth,
2	117838136	*PID1*	Meat quality and growth
4	9837443	*CDK6*	Associated with body length and heart girth in cattle
4	79562672	*GLI3*	Associated with growth traits in beef cattle
5	63619858	*ANKS1B*	Associated with body weight index and waist circumference in human
6	26386725	*MTTP*	Contains QTL for fatty acid composition in pigs and associated with lipid metabolism in Hanwoo
6	102610929	*ARHGAP24*	Related to growth traits in pigs
9	15582461	*SENP6*	Muscle lipid composition in *Bos taurus* cattle
11	16130458	*RASGRP3*	Associated with cell growth, fatty acid composition pig
12	2549494	*DIAPH3*	Associated with height, meat yield and longissimus dorsi in Korean cattle
12	11195490	*ELF1*	Growth and body composition traits in pigs, regulate intramuscular fat content (IMF)
13	82792074	*DOK5*	Potential roles in insulin and IGF-1 action
14	24306129	*XKR4*	Feed intake, average daily gain, birth weight, growth, muscle development, fat thickness in cattle
14	72494741	*CDH17*	Growth related in pigs
14	76053303	*DECR1*	Affects carcass quality traits in beef cattle
18	22191774	*FTO*	Associated with lean meat percentage in cattle
22	53457282	*LRRC2*	Associated with chest girth in pigs
23	9280385	*PPARD*	Regulates cholesterol metabolism

2003). For the last few decades, the Brown Hanwoo cattle have been subject to selection for growth and carcass quality traits. In addition to variation in production traits, the study breeds also exhibit distinct coat colors and patterns. More importantly, functional process analyses revealed that genes differentially differentiated between and Chikso and Hanwoo associated with relevant GO terms including, fatty acid beta-oxidation (*PPARD, DECR1, HSD17B4, HADHA*), adipose tissue development (*PPARD, ARID5B, FTO*), melanocyte differentiation (*MREG, GLI3, OCA2*), and melanosome transport (*BLOC1S3, MREG*) (Table 3).

For the Hanwoo-Heugu comparison, we detected genes under positive selection and previously known to affect beef production traits. Three candidate genes (*PRKAG2, GBA3,* and *BCAS3*) were shown to be associated with stature (Hawlader *et al.,* 2016; Fu *et al.,* 2014; Jennie *et al.,* 2011). Several of our candidate genes have been demonstrated to affect meat quality and feed efficiency (Table 4). *ACACB, PPARG, SENP6, PRKG1,* and *ANGPT1* have previously been identified to linked to fatty acid metabolism, adipose differentiation, muscle lipid composition, and marbling (Zhang1 *et al.,* 2017; Moisa *et al.,* 2013; Dunner *et al.,* 2013).

The results of the present study may provide some insight into the effect of artificial selection /demographic events in shaping the genetic diversity of Korean Peninsula cattle breeds. The smaller effect effective population sizes obtained for Chikso and Heugu over generations, warrants further strengthening of the ongoing conservation program. Following validation using more samples, SNPs which are identified as breed-specific can be used for product traceability and/or

Table 3. GO terms associated with candidate genes detected in Hanwoo-Chikso pair analysis

Term	Count	P-Value	Genes
GO:0007156~homophilic cell adhesion via plasma membrane adhesion molecules	7	0.008	*CDH12, CDH13, CDH17, ROBO1, PCDH15, CDH2, CDH23*
GO:0016339~calcium-dependent cell-cell adhesion via plasma membrane cell adhesion molecules	3	0.013	*CDH13, CDH17, CDH2*
GO:0006635~fatty acid beta-oxidation	4	0.020	*PPARD, DECR1, HSD17B4, HADHA*
GO:0001933~negative regulation of protein phosphorylation	4	0.025	*PID1, STK39, PARK2, PRR5L*
GO:0035249~synaptic transmission, glutamatergic	3	0.029	*CACNB4, PARK2, NAPB*
GO:0001954~positive regulation of cell-matrix adhesion	3	0.029	*CDH13, UTRN, CDK6*
GO:0032402~melanosome transport	3	0.029	*BLOC1S3, MREG*
GO:0048854~brain morphogenesis	3	0.029	*SLC6A4, MKKS, CDH2*
GO:0030318~melanocyte differentiation	3	0.037	*MREG, GLI3, OCA2*
GO:0060612~adipose tissue development	3	0.042	*PPARD, ARID5B, FTO*
GO:0007399~nervous system development	5	0.042	*PCSK2, APP, SRRM4, NAB1, SCN2A*
GO:0032728~positive regulation of interferon-beta production	3	0.046	*IFIH1, ZBTB20, POLR3C*
GO:0000187~activation of MAPK activity	4	0.048	*MAP3K7, LPAR3, ALK, MAP2K6*

Table 4. Candidate genes identified in the Heugu-Hanwoo pair comparison

Chr	Position	Gene	Function
3	83520921	*DOCK7*	Involved in piebald phenotype
4	114975718	*PRKAG2*	Association with body measurement and meat quality traits in cattle
6	43807650	*GBA3*	Associated with height
8	31195958	*MPDZ*	Feed conversion
8	36519484	*PTPRD*	Coat score
9	15505183	*SENP6*	Genes involved in muscle lipid composition
9	7946913	*BAI3*	Formation of adipose tissue.
10	49893042	*ANXA2*	Feed conversion efficiency in beef cattle Abo-Ismail et al., 2018)
14	59398170	*ANGPT1*	Fatty acid composition
14	80854140	*RALYL*	Associated with omega-6 fatty acids
17	16170473	*ACACB*	Fatty acid metabolism
19	11079076	*RPS6KB1*	Expressed in skeletal muscle
19	12159902	*BCAS3*	Stature in cattle
19	48571601	*MAP3K3*	Associated with human height
22	57415003	*PPARG*	Adipose differentiation
26	16856702	*SORBS1*	Linked to marbling
26	6912694	*PRKG1*	Feeding efficiency, tenderness, and residual feed intake

breed assignment. Given the evidence that the brown Hanwoo cattle have been intensively selected for beef traits over the last few decades, the genes identified in this study might be potential growth and carcass traits candidates for follow-up studies and subsequent inclusion in the selection program.

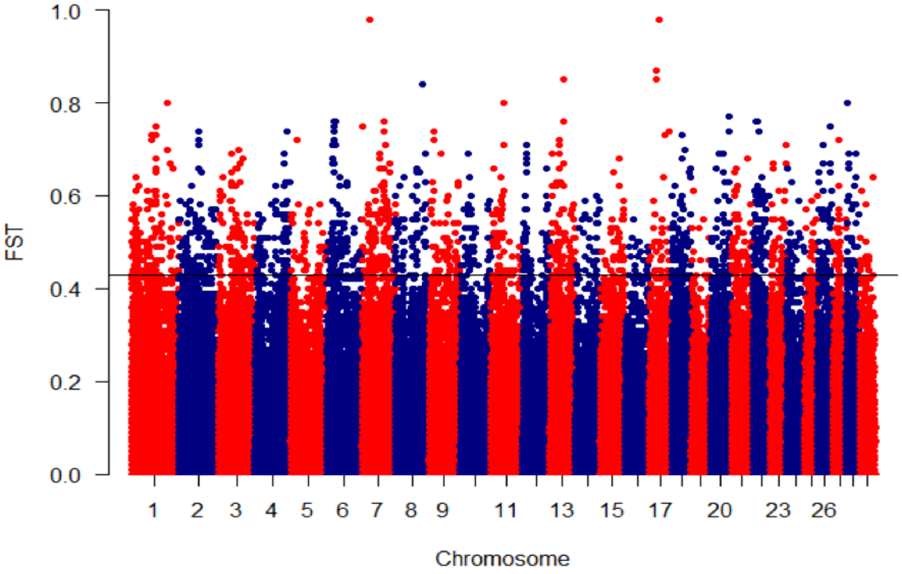

Figure 5. Manhattan plots of genome-wide distribution of FST values in Chikso-Hanwoo pair comparison

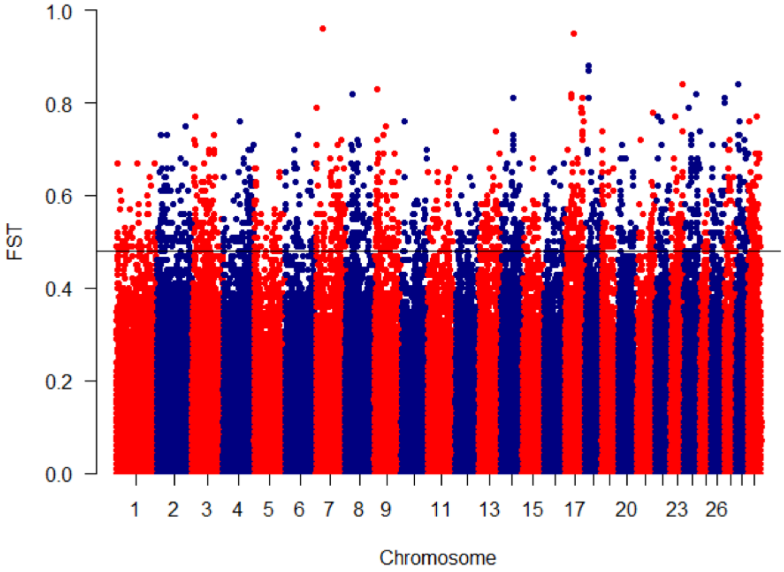

Figure 6. Manhattan plots of genome-wide distribution of FST values in Heugu-Hanwoo pair comparison

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References

Amills, M., O. Vidal, L. Varona, A. Tomas, M. Gil, A. Sanchez, and J. L. Noguera. 2005. Polymorphism of the pig 2,4-dienoyl CoA reductase 1 gene (DECR1) and its association with carcass and meat quality traits. J. Anim. Sci. 83:493–498.

Baek K, Baek J-H (2013) The transcription factors myeloid elf-1-like factor (MEF) and distal-less homeobox 5 (Dlx5) inversely regulate the differentiation of osteoblasts and adipocytes in bone marrow. Adipocyte 2: 50–54. 27.

Baik M., Nguyen TH., Jeong J.Y., Piao MY. and Kang H.J.2015. Effects of Castration on Expression of Lipid Metabolism Genes in the Liver of Korean Cattle. Asian-Australasian Journal of Animal Sciences, 28:127-134.

Bastin BC, Houser A, Bagley CP, Ely KM, Payton RR, Saxton AM, et al. A polymorphism in XKR4 is significantly associated with serum prolactin concentrations in beef cows grazing tall fescue. Anim Genet. 2014;45(3): 439–441. pmid:24666329.

Corominas J, Ramayo-Caldas Y, Puig-Oliveras A, Pe´rez-Montarelo D, Noguera JL, et al. (2013) Polymorphism in the ELOVL6 Gene Is Associated with a Major QTL Effect on Fatty Acid Composition in Pigs. PLoS ONE 8(1): e53687. doi: 10.1371/journal.pone.0053687.

Czech B, Frąszczak M, Mielczarek M, Szyda J (2018) Identification and annotation of breed-specific single nucleotide polymorphisms in *Bos taurus* genomes. PLoS ONE 13(6): e0198419. https://doi.org/10.1371/journal.pone.0198419

Decker JE, McKay SD, Rolf MM, Kim J, Alcalá AM, Sonstegard TS, Hanotte O, Götherström A, Seabury CM, Praharani L (2014) Worldwide patterns of ancestry, divergence, and admixture in domesticated cattle. *PLoS genetics* 10: e1004254.

Edea Z., Dadi H., Dessie T., Seung-Hwan L. and Kwan-Suk K. 2015. Genome-wide linkage disequilibrium analysis of indigenous cattle breeds of Ethiopia and Korea using different SNP genotyping BeadChips. Genes Genom. 37:759–765.

Espigolan R., Baldi F., Boligon A.A., Souza R.P., Gordo G.M., Tonussi R.L., Cardoso D.F., Oliveira H.N., Tonhati H., Sargolzaei M et al.2013. Study of whole genome linkage disequilibrium in Nellore cattle. BMC Genomics 14:305.

Fontanesi L., Scotti E., Buttazzoni L., Davoli R. & Russo V. (2009) The porcine fat mass and obesity associated (FTO) gene is associated with fat deposition in Italian Duroc pigs. Animal Genetics 40, 90–3.

Frayling T.M., Timpson N.J., Weedon M.N. et al. (2007) A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. Science 316, 889–94.

Han TW, Kim SK, Jeon Y.1966. The classification and distribution of Korean cattle tick. Rural Res Report, RDA.pp.91-103(in Korea).

Huang YZ., Wang KY., He H., Shen AQ., Lei CZ, Lan XY., Zhang CL and Chenn H. 2013. Haplotype distribution in the GLI3 gene and their associations with growth traits in cattle. Gene 513: 141–146.

Kim S., Cheong H.S., Shin H.D., Lee S.S., Roh H.J., Jeo D.Y and Cho Y. 2018. Genetic diversity and divergent among Korean cattle breeds assessed using a BovineHD single-nucleotide polymorphism chip. Asian -Australs J Anim Sci.31:1691-1699.

Lee S., Park SJ., Cheong JK., Ko JY., Bong J and Baik M.2017. Identification of circulating miRNA involved in meat yield of Korean cattle. Cell Biol Int, 41: 761–768.

Lee S-H, Park B-H, Sharma A, Dang C-G, Lee S-S, Choi T-J, Choy Y-H, Kim H-C, Jeon K-J, Kim S-D (2014a) Hanwoo cattle: origin, domestication, breeding strategies and genomic selection. Journal of animal science and technology 56: 1.

Lim D, Strucken EM, Choi BH, Chai HH, Cho YM, Jang GW, Kim T-H, Gondro C, Lee SH (2016) Genomic Footprints in Selected and Unselected Beef Cattle Breeds in Korea. PLOS ONE 11: e0151324.

Lindholm-Perry AK, Kuehn LA, Smith TP, Ferrell CL, Jenkins TG, Freetly HC, et al. A region on BTA14 that includes the positional candidate genes LYPLA1, XKR4 and TMEM68 is associated with feed intake and growth phenotypes in cattle. Anim Genet. 2012;43(2): 216–219. pmid:22404358.

Liu YF., Zan LS., Cui WT., Xin YP., Jiao Y and Li K. 2011. Molecular cloning, characterization and association analysis of the promoter region of the bovine CDK6 gene. *Genet.Mol.Res. 10: 1777-1786.*

Jin E, Liu J, Suehiro J, Yuan L, Okada Y, et al. (2009) Differential roles for ETS, CREB, and EGR binding sites in mediating VEGF receptor 1 expression in vivo. Blood 114: 5557–5566. doi: 10.1182/ blood-2009-05-220434. 26.

Marques E., Nkrumah JD., Sherman EL., and Moore SS. 2009. Polymorphisms in positional candidate genes on BTA14 and BTA26 affect carcass quality in beef cattle. J. Anim. Sci. 87:2475–2484.

Medeiros de Oliveira Silva R, Bonvino Stafuzza N, de Oliveira Fragomeni B, Miguel Ferreira de Camargo G, Matos Ceacero T, Noely dos Santos Gonçalves Cyrillo J, et al. (2017) Genome-Wide Association Study for Carcass Traits in an Experimental Nelore Cattle Population. PLoS ONE 12(1): e0169860.

Metzge J, Rau J., Naccache F., Conn LB., Lindgren G and Distl. 2018. Genome data uncover four synergistic key regulators for extremely small body size in horses. BMC Genomics, 19:492.

Park B, Choi T, Kim S, Oh SH (2013b) National Genetic Evaluation (System) of Hanwoo (Korean Native Cattle). Asian-Australasian Journal of Animal Sciences 26: 151-156.

Porto Neto LR, Bunch RJ, Harrison BE, Barendse W. Variation in the XKR4 gene was significantly associated with subcutaneous rump fat thickness in indicine and composite cattle. Anim Genet. 2012;43(6): 785–789. pmid:22497494.

Ramayo-Caldas Y, Fortes MRS, Hudson NJ, Porto-Neto LR, Bolormaa S, et al. (2014) A marker derived gene network reveals the regulatory role of PPARGC1A, HNF4G and FOXP3in intramuscular fat deposition of beef cattle. J Anim Sci. A.

Rempel L.A., Casas E., Shackelford S.D. & Wheeler T.L. (2012) Relationship of polymorphisms within metabolic genes and carcass traits in crossbred beef cattle. Journal of Animal Science 90, 1311–6.

Rudra D, deRoos P, Chaudhry A, Niec RE, Arvey A, et al. (2012) Transcription factor Foxp3 and its protein partners form a complex regulatory network. Nat Immunol 13: 1010–1019. doi: 10.1038/ni.2402.

Skok DJ., Kunej T., Kovac M., Malovrh S., Potocnik K., Petric K., Zgur S., Dovc P. and Horvat S. 2015. FTO gene variants are associated with growth and carcass traits incattle. Animal Genetics,47:219-222.

Suh S, Kim Y-S, Cho C-Y, Byun M-J, Choi S-B, Ko Y-G, Lee CW, Jung K-S, Bae KH, Kim J-H (2014) Assessment of Genetic Diversity, Relationships and Structure among Korean Native Cattle Breeds Using Microsatellite Markers. *Asian-Australasian Journal of Animal Sciences* 27: 1548-1553