



## Single Nucleotide Polymorphism of TBC1D1 Gene Association with Growth Traits and Serum Clinical-Chemical Traits in Chicken

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**ABSTRACT** TBC1D1 gene has known functional effects on body energy homeostasis and glucose uptake pathway in skeletal muscle tissue. This biological function is reported to have significant effects on traits of growth and meat quality in chicken. In this study, we focused on two single nucleotide polymorphisms (SNPs) (g.70179137A>G and g.70175861T>C) identified through SNP annotation information of Korean native chicken and previous literature for TBC1D1 in chicken. Association of SNPs in TBC1D1 with growth and serum clinical-chemical traits were evaluated. A total of 584 male and female birds from five Korean native chicken lines were used in the study. The SNP1 (g.70179137A>G) is located in intron 11 and SNP2 (g.70175861T>C) is a non-synonymous missense mutation in exon 10, responsible for the amino acid change from Methionine to Valine. The A allele of SNP1 and T allele of SNP2 had the highest allele frequencies. Both SNPs indicated moderate polymorphism information content values ( $0.25 < PIC < 0.5$ ). Association results shown that SNP1 was significantly associated with BW00, BW20, GR14-16 and carcass weight ( $P < 0.05$ ). The AA genotype had higher value for all these traits except BW00. Whereas, genotype GG have lower values for BW20, GR14-16, GR18-20 and carcass weight. The sGOT level was significant with SNP1 but not with the SNP2. The GG genotype had the highest sGOT value and AG reported the lowest. BW20 was significantly associated with SNP2 ( $P < 0.05$ ). The body weight and carcass weight values of CC and TC genotypes were higher than those of TT genotype.

(Key words: association, chicken, growth trait, TBC1D1 gene)

## INTRODUCTION

Application of genetic markers for precise and fast identification of potential candidate genes for quantitative traits in livestock have been reported in several studies (Hocking, 2005; Zhu and Zhao, 2007). Identification and application of such genes for selection of livestock through marker assistance selection (MAS) is now become a norm in livestock breeding program (Dekkers and van der Werf, 2007). This is because the use of genomic information can increase accuracy and selection rate. Therefore, increase the selection response. Van der Beek and van Arendonk (1996) have estimated that an additional total selection response of 6% to 13% when using MAS that incorporate the markers linked the quantitative trait loci (QTL) after five generation of selection. More recently, genome wide association test to identify the

causal mutation and underlying genes, which describe the large variation of production traits in livestock including poultry, were reported for many commercial and domestic crossbreeds (Cahyadi et al., 2014). Particularly, QTLs that highly responsible for chicken growth and carcass traits were located on several major chromosomal regions, GGA1, 2, and 4 for the broiler Leghorn cross (Zhou et al., 2006), GGA1, 2, 4, 10 for Hampshire and white Leghorn chicken line (Nassar, Goraga and Brockmann, 2015), GGA3, 4, 19 and 20 for Korean native chicken lines (Cahyadi et al., 2016).

Among the reported candidate genes from several QTLs in the distal region of GGA4 and by genome wide studies, the TBC1D1 gene was identified as a one of functional candidate genes that responsible for obesity, growth in mammals, and livestock animals including chicken (Gu et al., 2011; Nassar et al., 2015). During the domestication of chicken and sub-

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sequent specialization to broiler and layer lines, some of the genes in domestic lines were undergone important selective sweep related to the growth. Recent whole-genome resequencing studies identified that the TBC1D1 gene was among those reported sweeps for commercial broilers (Rubin et al., 2010; Fan et al., 2013).

The Rab-GTPase-activating protein (TBC1D1) was first revealed as a protein, regulating cell differentiation and growth in a screen of a murine mast cell library (Dokas, 2016). TBC1D1 belongs to the Rab-GAP protein family that transmitting specific signals that stimulate biological effects on glucose uptake in skeletal muscle. Variants in the TBC1D1 gene have been significantly associated with fat and lean meat deposition and energy homeostasis in pig (Fontanesi et al., 2011; Howard et al., 2015). Similarly, in rabbit variant (c.214G>A) in exon 1 was significantly associated with body weight at 35 and 56 days (Yang et al., 2013). In several other researches, variants in this gene were associated with obesity-related traits in mice and body mass index in human (Stone et al., 2006; Dokas et al., 2016). Possible functional involvement of TBC1D1 gene in chicken was described in Wang et al. (2014). A significant genomic region that affecting growth from 5 to 20 weeks age was recorded at the lateral region of GGA4, between 153 and 159 cM (61.5~88.4 Mb size) harbor the TBC1D1 gene (Nassar et al., 2015).

Therefore, the aim of this current study was to investigate effect of two SNP variant on growth traits (zero weeks to 20 weeks, weight gain from GR0-2 weeks~GR18-20 weeks), weight at slaughter, carcass weight and serum chemical traits in Korean native chicken (KNC).

## MATERIAL AND METHODS

### 1. Animal and Data Collection

This experiment was performed in agreement with “The Guide for the Care and Use of Laboratory Animals,” published by the Institutional Animal Care and Use Committee of the National Institute of Animal Science (NIAS) (2012-C037), Republic of Korea. A total of 597 chickens of F<sub>1</sub> generation representing 70 half sib families from 88 (F<sub>0</sub>) parents of Korean native chicken (15 sires & 73 Dams) were used. Finally, we used 584 birds from total of 597 birds; Gray-Brown (G=110), Black (L=88), Red-Brown (R=135), White (W=121) and Yellow-Brown (Y=130) for the analysis. All the birds were reared with the same feeding and environment conditions provided by the NIAS. Growth traits; body weight (BW) from zero weeks to 20 weeks, weight at slaughter (recorded after given fasting time) were reported. Weight gain (GR) at 2 week interval was calculated. Carcass weight and eight serum clinical-chemical traits were measured and described in previous study are included for this study (Seo et al., 2016).

### 2. Genotyping using KASP Assay

Genomic DNA was isolated from the whole blood samples following standard manual procedure and concentrations were measured using a NanoDrop<sup>®</sup> 2000C spectrophotometer (Thermo Scientific, USA). The TBC1D1 gene was selected as a functional candidate gene in QTL region that have identified in several studies and SNP variations described in this study were obtained via filtering the Korean native chicken whole genome SNP annotation information. SNP target specific primers were prepared for KASP genotyping assay (Table 1). Both parent and progeny samples were genotyped by KASP genotyping assay and compared to validate the genotype states of F<sub>1</sub> birds.

### 3. Statistical Analysis

Genotype data and quantitative data were prepared in excel

**Table 1.** Primer information for SNP genotyping for chicken TBC1D1 gene by KASP genotyping assay

Gene	Marker	rs_number	Mutation type	Forward primer X, Y (5'-3')	Reverse primer (5'-3')	Fluorescent color (wild/mutant)
TBC1D1 gene	Primer1	rs80645709	Intron var	CAAAATTATGGTCAGAGGCAATAAACACA/ AAATTATGGTCAGAGGCAATAAACACG	GATCTCTGACGGAA TCGTTTGAAAGTATT	A / G (FAM/HEX)
	Primer2	rs14742436	Missense	GGTCACTGGAAAGATCACCCAC/ GGTCACTGGAAAGATCACCCAT	GAGAATGCTGTCAA GAGCAGTGGAT	C / T (FAM/HEX)

and R softwares. Descriptive statistics for phenotypic data were obtained using MINITAB version 14 (MINITAB Inc., USA). Gene frequencies were determined for each SNP in total population by using population genetics package “genetics” implemented in R (Warnes, 2015). Statistical analyses for association between meat quality traits and genotypes were performed based on mean adjusted performance of the progeny using general linear model procedure (GLM) in MINITAB version 14. Association analyses were performed separately using single SNP approach, following the linear mixed models describes in below.

$$Y_{ijklmn} = \mu + S_i + L_j + B_k + \text{Sire}_m (\text{line}) + \text{Dam}_n (\text{line, Sire}) + M_m + e_{ijklmn} \quad (\text{Model I})$$

Where,  $Y_{ijklmn}$  was the trait measured on each animal.  $\mu$  was the overall mean of observation,  $S_i$  was gender effect,  $L_j$  was the line effect,  $B_k$  was fixed effect due to the  $K^{\text{th}}$  batch,  $\text{Sire}_m (\text{line})$  was the fixed effect of  $m^{\text{th}}$  sire nested in  $j^{\text{th}}$  line.  $\text{Dam}_n (\text{line, sire})$  was the effect of  $n^{\text{th}}$  dams nested in  $j^{\text{th}}$  line and  $m^{\text{th}}$  sire in the population and  $M_m$  was the fixed effect of  $m^{\text{th}}$  genotype.  $e_{ijklmn}$  was the random residual error. Model I was used for growth traits and weight at slaughter. For the serum clinical-chemical traits, following model (II) was used with fixed effect of fasting time ( $FT_1$ ). Statistical significance was tested and pairwise comparison of means were obtained using Tukey test. Mean differences were considered significant at 95% ( $P < 0.05$ ) confidence level.

$$Y_{ijklmn} = \mu + S_i + L_j + B_k + FT_1 + \text{Sire}_m (\text{line}) + \text{Dam}_n (\text{line, Sire}) + M_m + e_{ijklmn} \quad (\text{Model II})$$

## RESULTS AND DISCUSSION

### 1. Genotype and Allele Frequencies

Two selected SNPs from the KNC SNP annotation data (g.70179137A>G and g.70175861T>C) were evaluated. Table 2 described the genotype and allele frequencies of two SNPs. For SNP1 (A/G), A allele has highest allele frequency of 0.54 and for the SNP2 (T/C) C allele had the highest value (0.56). Especially, the SNP2 is a nonsynonymous missense mutation responsible for amino acid change from Methionine to Valine (ATG/GTG) (<https://asia.ensembl.org/>). Previously, Wang et al. (2014) reported the same SNP2 (g.69340192G>A), but in the form of complementary strand that may be based on the *Gallus gallus* 4.0 reference genome. Compare to our population, allele frequencies of SNP2 in his study population were similar for both allele (0.5). In our study, we reported moderate polymorphic information content (PIC) values for both SNPs (0.374 and 0.372 respectively).

### 2. Association Analysis

There are very few studies discussed the TBC1D1 gene polymorphisms and their potential associations with growth traits in chicken despite the potential QTL region that included the TBC1D1 as a candidate gene. Therefore, our objective of this study is to evaluate the selected two SNPs, especially the effect of SNP2 that has been shown significant relationship in Erlang chicken (Wang et al., 2014). We used body weight (BW) data from zero to 20 weeks of age and weight gain calculated at the two weeks interval. In addition, weight at slaughter (SLW) and carcass weight (CW) and eight serum clinical-chemical traits were included. The descriptive statistics

**Table 2.** Genotype and allele frequencies for SNPs in TBC1D1 gene

SNP marker	Type	Genotype frequency			Allele frequency		PIC value <sup>1</sup>
		AA	AG	GG	A	G	
SNP1	Intron var.						0.374
g.70179137A>G rs80645709		181(0.31)	261(0.45)	139(0.24)	623(0.54)	539(0.46)	
SNP2	Missense. (ATG/GTG)						0.372
g.70175861T>C rs14742436		206(0.35)	235(0.40)	140(0.24)	647(0.56)	515(0.44)	

<sup>1</sup>PIC: Polymorphic information content.

for all the traits described in Table 3 & Table 4, respectively.

Least square means of traits after corrected for all the fixed effects were statistically evaluated. The growth trait results showed that SNP1 was significant for BW00, BW20, GR14-16, and CW ( $P < 0.05$ ) (Table 5). SNP1 given significant association with Glutamate Oxaloacetate transaminase (sGOT) level in blood serum but not with the SNP2 (Table 6).

However, the SNP 2 was reported significant association

**Table 3.** Descriptive statistics for growth traits in Korean native chicken

Trait (g) <sup>1</sup>	N	Mean	±SE of mean
BW00	581	38.39	0.21
BW02	574	143.76	1.03
BW04	579	265.52	2.91
BW06	581	426.47	5.42
BW08	579	607.09	8.08
BW10	580	767.40	9.17
BW12	579	991.30	11.50
BW14	580	1,179.40	12.30
BW16	581	1,383.00	13.90
BW18	581	1,587.80	14.30
BW20	581	1,780.20	15.30
SLW	581	1,694.30	15.10
CW	577	998.95	9.94
GR0-2	574	105.41	0.98
GR2-4	580	123.01	2.03
GR4-6	580	161.46	2.75
GR6-8	579	180.73	2.98
GR8-10	577	160.44	2.88
GR10-12	578	223.54	3.89
GR12-14	578	188.25	3.76
GR14-16	572	209.24	3.22
GR16-18	578	205.99	4.56
GR18-20	579	190.98	3.04

<sup>1</sup> body weight from zero weeks to 20 weeks (g), SLW: weight at slaughter (g), CW: Carcass weight (g), GR0-2~GR18-20: weight gain (g).

**Table 4.** Descriptive statistics for serum clinical-chemical traits in Korean native chicken

Trait	N	Mean	±SE of mean
Glu	581	255.97	1.12
T-Pro	579	4.2154	0.0260
GPT	581	2.9254	0.0173
Cre	581	-0.228	0.0134
HDL_C	581	96.41	1.25
T-Cho	579	134.8	1.53
GOT	579	5.3959	0.00950
Amy	572	5.3681	0.0130

Glu: glucose (mg/dL), T-Pro: total protein (g/dL), GPT: glutamic-pyruvic transaminase (IU/L), Cre: creatinine(mg/dL), HDL\_C: high density lipoprotein cholesterol (mg/dL), T-Cho: total cholesterol (mg/dL), GOT: glutamic oxaloacetic transaminase, Amy: amylase (IU/L).

with BW20 ( $P < 0.05$ ) (Table 5). Interestingly, the SNP2 reported to have significant associated with live weight, carcass weight, and several other meat quality traits in Erlang mountainous chicken (Wang et al., 2014). Most of the body weight traits and serum clinical-chemical traits were not significant (Table 6). Moreover, serum glucose level was not significant for both SNPs.

Peng et al. (2015) showed that higher TBC1D1 mRNA expression in thigh muscle, and abdominal fat at 10 and 13 weeks of age in male chicken compare to that of female birds. To evaluate sex effects on this gene, the interaction between sex, line and genotype was tested. However, no significant relationship was identified.

In our study population, SNP1 for BW20, GR14-16, GR18-20 and CW, genotype AA have higher value. Whereas, GG genotype was responsible for lower values of these traits. AG genotype shown average values for these traits. This indicated that A allele has the favorable effects on the growth traits.

On the other hand, CC genotype of SNP2 was shown higher value for BW20, GR14-16 and CW. Moreover, TT was responsible for the lowest value and genotype TC was moderate effect. Therefore, it is clear that C allele is favorable for traits in F1 progeny of KNC. Similarly, Wang

**Table 5.** Least square means for growth traits in Korean native chicken

<sup>1</sup> Trait	<sup>2</sup> Least square mean ( $\pm$ SE)			<i>P</i> -value
	AA	AG	GG	
rs80645709 (SNP1)				
BW00	38.40 $\pm$ 0.2265 <sup>b</sup>	38.48 $\pm$ 0.1769 <sup>b</sup>	39.25 $\pm$ 0.266 <sup>a</sup>	<b>0.025</b>
BW20	1,797 $\pm$ 18.43 <sup>a</sup>	1,776 $\pm$ 14.39 <sup>a</sup>	1,719 $\pm$ 21.69 <sup>b</sup>	<b>0.027</b>
GR14-16	226.8 $\pm$ 6.37 <sup>a</sup>	206.7 $\pm$ 5.06 <sup>b</sup>	192.5 $\pm$ 7.64 <sup>b</sup>	<b>0.004</b>
GR18-20	204.4 $\pm$ 6.56	190.6 $\pm$ 5.10	179.3 $\pm$ 7.688	0.06
CW	1,011.8 $\pm$ 12.45 <sup>a</sup>	989.9 $\pm$ 9.72 <sup>ab</sup>	959.4 $\pm$ 14.62 <sup>b</sup>	<b>0.036</b>
rs14742436 (SNP2)				
BW20 (g)	1,795 $\pm$ 16.90 <sup>a</sup>	1,773 $\pm$ 15.37 <sup>ab</sup>	1,724 $\pm$ 21.44 <sup>b</sup>	<b>0.039</b>
GR14-16	218.4 $\pm$ 5.90	210.5 $\pm$ 5.41	196.6 $\pm$ 7.54	0.08
CW	1,009.7 $\pm$ 11.41 <sup>a</sup>	987.4 $\pm$ 10.39 <sup>ab</sup>	962.7 $\pm$ 14.45 <sup>b</sup>	0.048

<sup>1</sup> BW00: body weight at zero weeks (g), BW20: body weight at 20 weeks (g), CW: carcass weight (g), GR14-16: weight gain from 14weeks to 16 weeks (g), GR18-20: weight gain from 18 weeks to 20 weeks (g).

<sup>2</sup> Least square means for growth traits adjusted for fixed effect.

<sup>a,b</sup> Means within a row with no common superscript differ significantly ( $P < 0.05$ ).

**Table 6.** Least square means for serum clinical-chemical traits in Korean native chicken

Gene/ marker	<sup>1</sup> Trait	<sup>2</sup> Least square mean ( $\pm$ SE)			Association <i>P</i> -value
		AA	AG	GG	
SNP1 rs80645709	Glu	256.7 $\pm$ 6.406	256.4 $\pm$ 5.055	240.8 $\pm$ 9.532	0.633
	T-Pro	4.026 $\pm$ 0.150	4.249 $\pm$ 0.118	4.196 $\pm$ 0.223	0.224
	GPT	2.873 $\pm$ 0.089	2.836 $\pm$ 0.071	3.094 $\pm$ 0.133	0.395
	Cre	-0.241 $\pm$ 0.071	-0.373 $\pm$ 0.056	-0.165 $\pm$ 0.105	0.085
	HDL_C	98.38 $\pm$ 6.247	104.31 $\pm$ 4.93	95.57 $\pm$ 9.295	0.974
	T-Cho	129.5 $\pm$ 8.179	143.0 $\pm$ 6.479	150.2 $\pm$ 12.169	0.489
	GOT	5.439 $\pm$ 0.051 <sup>b</sup>	5.403 $\pm$ 0.039 <sup>a</sup>	5.441 $\pm$ 0.075 <sup>b</sup>	<b>0.018</b>
	Amy	5.294 $\pm$ 0.070	5.275 $\pm$ 0.056	5.405 $\pm$ 0.106	0.768
SNP2 rs14742436					
	Glu	256.5 $\pm$ 4.599	239.3 $\pm$ 9.479	258.0 $\pm$ 6.920	0.851
	T-Pro	4.356 $\pm$ 0.108	3.925 $\pm$ 0.222	4.189 $\pm$ 0.162	0.172
	GPT	2.985 $\pm$ 0.064	3.018 $\pm$ 0.132	2.799 $\pm$ 0.097	0.149
	Cre	-0.245 $\pm$ 0.051	-0.261 $\pm$ 0.105	-0.273 $\pm$ 0.07	0.847
	HDL_C	101.86 $\pm$ 4.484	87.78 $\pm$ 9.243	108.61 $\pm$ 6.748	0.727
	T-Cho	139.6 $\pm$ 5.872	143.5 $\pm$ 12.102	139.7 $\pm$ 8.845	0.779
	GOT	5.424 $\pm$ 0.036	5.433 $\pm$ 0.074	5.426 $\pm$ 0.054	0.872
Amy	5.359 $\pm$ 0.050	5.343 $\pm$ 0.105	5.271 $\pm$ 0.077	0.302	

<sup>1</sup> Glu: glucose (mg/dL), T-Pro: total protein (g/dL), GPT: glutamic-pyruvic transaminase (IU/L), Cre: creatinine (mg/dL), HDL\_C: high density lipoprotein cholesterol (mg/dL), T-Cho: total cholesterol (mg/dL), GOT: glutamic oxaloacetic transaminase, Amy: amylase (IU/L).

<sup>2</sup> Least square means for serum clinical-chemical traits adjusted for fixed effect.

<sup>a,b</sup> Means within a row with no common superscript differ significantly ( $P < 0.05$ ).

et al. (2014) reported that heterozygous state of this SNP can give higher live weight, carcass weight, eviscerated weight and breast muscle weight.

Previous QTL and genome wide association studies in chicken described elsewhere (Gu et al., 2011; Nassar et al., 2013) identified TBC1D1 gene located in the confidence interval of QTL region on GGA4, associated with the visceral, subcutaneous neck and total adipose tissue, body weight and growth rate during different stage of their development. This region also affects the fat mass and body mass at 20 weeks of age (Nassar et al., 2015). Interestingly, in several other studies reported, QTL for growth and body weight in the same region where that include the TBC1D1 gene (Zhou et al., 2006; Ambo et al., 2009). Moreover, this gene has critical roles in regulation of glucose and lipid metabolism in skeletal muscle and body energy homeostasis (Fontanesi et al., 2013). TBC1D1 gene also shows tissue specific expression in several other tissues such as brain, breast, heart and liver (Stone et al., 2006). Investigation on the role of TBC1D1 in insulin signaling and metabolism in skeletal muscle describe that unphosphorylated TBC1D1 state tightly bind to the GLUT4 molecules and reduce the rate of glucose transport into cell (Sano et al., 2003; Taniguchi et al., 2006). In contrast, TBC1D1 has a negative impact on the uptake of fatty acids and fatty acid oxidation. Moreover, TBC1D1 was identified as a third most significant marker associated with fatness in pig (Fontanesi et al., 2011, 2012). These findings suggest that variations in TBC1D1 gene may affect the growth and carcass traits.

Serum Glutamic Oxaloacetic transaminase (sGOT) is also known as aspartate transaminase (AST) is responsible for catalyzes the reversible transamination between L-aspartate and 2-oxoglutarate to form oxaloacetate and glutamate. sGOT found in liver, heart, skeletal muscle and brain where it involves in glutamine-cycling pathway (Sookoian and Pirola, 2012). Several environment factors other than genetic effects were reported for elevated GOT level in serum in chicken (Elaroussi et al., 2008). Moreover, authors reported that a significant association with insulin resistance with glutamine, glutamate and the ratio between glutamine and glutamate. Thereby, involvement of sGOT in glutamine-cycling pathway (Sookoian and Pirola, 2012).

In our study, we have focused only two SNPs in TBC1D1 gene. Nevertheless, several of other SNPs in TBC1D1 gene are remained to analyze for their effects on growth, meat quality traits in chicken. Based on the current results, we can suggest that TBC1D1 gene have significant effect on growth traits. Therefore, more association studies required to evaluate and validate the effect of TBC1D1 gene on growth traits in chicken.

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