Single nucleotide polymorphisms associated with growth traits in Jinghai yellow chickens

M.A. Abdalhag[1,2], T. Zhang[1,2], Q.C. Fan[1,2], X.Q. Zhang[1,2], G.X. Zhang[1,2], J.Y. Wang[1,2], Y. Wei[1,2] and Y.J. Wang[3]

[1]College of Animal Science and Technology, Yangzhou University, Yangzhou, Jiangsu, China
[2]Key Laboratory for Animal Genetics, Breeding, Reproduction and Molecular Design of Jiangsu Province, Yangzhou, Jiangsu, China
[3]Jiangsu Jinghai Poultry Group Co., Ltd., Nantong, Jiangsu, China

Corresponding author: J.Y. Wang
E-mail: jywang@yzu.edu.cn

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ABSTRACT. Body weight is one of the most important economic traits in the poultry industry. In the present study, a custom SNP Beadchip was used to analyze the association between those 15 SNPs and 12 growth traits of Jinghai yellow chickens, and other important genetic parameters were also calculated and analyzed. The results indicated that nine of the 15 SNPs were associated with growth traits in Jinghai yellow chickens ($P < 0.05$), and the identified SNPs were also in linkage disequilibrium. Five of the nine identified SNPs were mainly associated with all of the growth traits, which indicated that those five SNPs might have significant influence on Jinghai yellow chicken growth traits. Polymorphism information content (PIC) analyses indicated that five of the nine SNPs exhibited moderate polymorphism ($0.25 < PIC < 0.5$), which reflected intermediate genetic diversity. Six candidate genes surrounding the significant SNPs were obtained and subjected to Gene Ontology annotation analyses and pathway analyses. The functions of six important candidate genes (*SETDB2*, *ATP7B*, *INTS6*, *KPNA3*, *DLEU7*, and *FOXO1A*) were discussed. The present study provided basic data for

marker-assisted selection in Jinghai yellow chickens.

Key words: Jinghai yellow chicken; Growth traits; Linkage disequilibrium; GWAS

INTRODUCTION

In the poultry industry, growth is considered one of the most important economic traits. Much effort has been invested to improve growth traits, especially regarding genetic improvement. Therefore, work towards the genetic improvement of growth traits is essential, and the genetic improvement in chicken growth traits has made great progress during the past few years. However, most of the work was conducted using traditional breeding methods. Marker-assisted selection (MAS) is a new method based on molecular markers, which can shorten the breeding process and save a lot of time and money (Lu and Wu, 2002). Therefore, it is essential to exploit and identify new markers that could be used in breeding work.

Many traditional methods are currently used to detect SNPs, including DNA sequencing, Restriction Fragment Length Polymorphism (RFLP), Single Stranded Conformational Polymorphism (SSCP), and denaturing high performance liquid chromatography (DHPLC); however, these methods lack speed, efficiency, and automation. Recently developed DNA Beadchip technology is a method used to detect DNA sequence variation, and it is widely used in studies of human disease and economically important animal traits. In chickens, many genome-wide association studies (GWAS) were conducted using the Illumina 60K SNP Beadchip. Using this method, major loci associated with growth (Gu et al., 2011; Xie et al., 2012), egg production (Liu et al., 2011; Wolc et al., 2012), rumpless and ear-tufted traits (Noorai et al., 2012), body composition and meat quality (Liu et al., 2013), resistance to Marek's disease (Li et al., 2013), and immune responses to Newcastle disease virus (Luo et al., 2013) were identified.

A previous study observed 15 SNPs (Table 1), detected by SNP Beadchip analysis, in a 168.5-170.0 Mb region of *GGA1* that influenced chicken growth traits ($P < 0.05$) (Xie et al., 2012). In the present study, a custom SNP Beadchip was used to analyze the association between those 15 SNPs and 12 growth traits of Jinghai yellow chickens. Furthermore, major population genetic parameters were calculated, including gene frequency, genotype frequency, and effective number of alleles, and the linkage disequilibrium (LD) and haplotypes of the SNPs were also analyzed. Ensembl and NCBI were used to obtain genes within this region with 1-Mb windows surrounding each SNP (SNP position ± 0.5 Mb). We aimed to identify new SNPs and candidate genes associated with growth traits and to provide basic data for MAS of Jinghai yellow chickens.

MATERIAL AND METHODS

Population and sample collection

A total of 396 blood samples were collected from female Jinghai yellow chickens, and all samples were randomly selected from the same batch at the Jiangsu Jinghai Poultry Industry Group Co., Ltd. All experimental chickens were hatched on the same day, and were subsequently raised in floor pens with access to water and feed (commercial diets meeting NCR requirements). Bodyweight data were recorded at the following ages (in weeks): 2 (BW2), 4 (BW4), 6 (BW6), 8

(BW8), 10 (BW10), 12 (BW12), 14 (BW14), and 16 (BW16). Average daily weight gains between ages 0-4 (ADG4), 4-8 (ADG8), 8-12 (ADG12), and 12-16 (ADG16) weeks were calculated, and the basic growth trait statistics are shown in Table 2.

Table 1. Locations and relevant traits of 15 SNPs.

SNP ID	Chromosome	Position (bp)
rs316142388	1	168504143
rs15497877	1	168589760
rs15497910	1	168609931
rs314214528	1	168841831
rs13972304	1	168931358
rs313583074	1	168993046
rs13553164	1	169026310
rs14917305	1	169093530
rs317063416	1	169121392
rs14917647	1	169403027
rs13553485	1	169614824
rs315321005	1	169803697
rs13973515	1	169868287
rs314628319	1	169941464
rs314967487	1	169978701

Table 2. Basic growth-trait statistics for the experimental chickens.

Traits	Sample size	Maximum	Minimum	Mean	Standard deviation
BW2	300	126.0	40.0	85.6	13.5
BW4	348	324.0	106.0	205.3	29.9
BW6	343	495.0	200.0	330.2	52.1
BW8	293	695.0	310.0	513.5	72.7
BW10	288	1290.0	405.0	706.4	106.7
BW12	273	1170.0	605.0	870.7	100.5
BW14	335	1480.0	680.0	1042.3	113.8
BW16	398	1502.0	725.0	1123.5	124.8
ADG4	300	20.7	6.4	12.3	5.2
ADG8	255	36.6	7.9	22.0	4.3
ADG12	252	45.0	7.5	25.7	4.8
ADG16	271	41.1	5.6	18.2	5.2

The unit of body weight (BW) is g. The unit of average daily weight gain (ADG) is g/day. BW2, BW4, BW6, BW8, BW10, BW12, BW14, and BW16 are the body weights at ages 2, 4, 6, 8, 10, 12, 14, and 16 weeks, respectively. ADG4, ADG8, ADG12, and ADG16 are the average daily gains during weeks 0-4, 4-8, 8-12, and 12-16, respectively.

DNA extraction and genotyping

Genomic DNA was extracted using the Dzup Genomic DNA Isolation Reagent Kit from Sangon Biotech Co., Ltd. (Shanghai, China). The DNA concentration and quality were quantified by spectrophotometry and agarose gel electrophoresis. The quality control criterion was the genome DNA concentration >100 ng/mL, $1.7 < OD_{260}/OD_{280}$ value < 1.8. Subsequently, the qualified DNA samples were sent to DNA LandMarks Inc. (Quebec, Canada) for genotyping using the custom SNP Beadchip. Genotyping was carried out according to the Beadchip Assay Kit (Illumina, USA) protocol. The genotypes of the 15 SNPs were obtained by the SNP ID.

Statistical analysis

Statistical analyses were conducted using SPSS 19.0 version, and the general linear

model (GLM) procedure was used to analyze the associations between 155 SNPs and 12 growth traits according to the following model:

$$Y = \mu + G_i + e_{ij}$$

where, Y is the corrected phenotypic value of the growth traits, μ is the overall mean, G_i is the single-locus SNP genotype effect, and e_{ij} is a random residual.

Allele frequency, genotype frequency, efficient allelic number (N_E), polymorphism information content (PIC), and chi-square tests were calculated using the POPGENE program (Zane et al., 2002). LD was calculated using the SHEsis program (Shi et al., 2005), and haplotypes were analyzed using Phase version 2.1.

RESULTS

Association analysis

The results of the association analysis between SNPs and growth traits showed that nine out of the 15 SNPs were associated with Jinghai yellow chicken growth traits ($P < 0.05$) (Table 3). Seven of the nine SNPs were found to be associated with more than two traits, and the other two SNPs (rs14917305 and rs13553485) effected ADG16 and BW2, respectively. The results indicated that SNPs rs15497877, rs13972304, rs13553164, rs14917647, and rs13973515 were associated with body weight at both the early (2-8 weeks) and late (10-16 weeks) growth stages. SNPs rs314214528 and rs13553485 were associated with body weight at the early growth stage (2-8 weeks), while rs316142388 was strongly associated with body weight at the late growth stage (10-16 weeks). SNPs rs15497877, rs13972304, and rs14917647 were associated with average daily weight gains at both early (4-8 weeks) and late (12-16 weeks) growth stages. Moreover, SNPs rs314214528 and rs13973515, were associated with average daily weight gains at the early growth stage (4-8 weeks), while rs14917305 was associated with average daily weight gains at the late growth stage (12-16 weeks).

Table 3. Association analysis between 9 SNPs and 12 growth traits.

SNP ID	BW2	BW4	BW6	BW8	BW10	BW12	BW14	BW16	ADG4	ADG8	ADG12	ADG16
rs316142388	0.367	0.372	0.322	0.791	0.402	0.021*	0.023*	0.001*	0.146	0.681	0.094	0.366
rs15497877	0.368	0.181	0.026*	0.040*	0.113	0.002*	0.007*	0.012	0.327	0.026*	0.033*	0.354
rs314214528	0.127	0.007*	0.002*	0.450	0.131	0.270	0.704	0.219	0.026*	0.842	0.398	0.737
rs13972304	0.930	0.094	0.001*	0.197	0.302	0.247	0.172	0.009*	0.030*	0.080*	0.761	0.040*
rs13553164	0.035*	0.223	0.248	0.224	0.025*	0.882	0.878	0.523	0.174	0.465	0.511	0.040*
rs14917305	0.198	0.436	0.176	0.161	0.696	0.531	0.570	0.188	0.263	0.852	0.354	0.011*
rs14917647	0.057	0.004	0.364	0.019*	0.610	0.067	0.036*	0.002*	0.011*	0.104	0.069	0.005*
rs13553485	0.025*	0.569	0.257	0.932	0.775	0.586	0.519	0.062	0.302	0.870	0.643	0.056
rs13973515	0.360	0.266	0.141	0.022*	0.041*	0.509	0.013*	0.013*	0.764	0.034*	0.754	0.130

*Indicates significance ($P < 0.05$).

Genetic parameters of significant SNPs

Allele frequency, genotype frequency, N_E, PIC, and chi-square tests were calculated (Table 4A and B). The results showed that SNPs rs13553164, rs14917647, and rs13973515 had missing

genotypes. PIC analysis results indicated that SNPs rs316142388, rs314214528, rs13972304, and rs13553485 exhibited low polymorphism (PIC < 0.25), and the other five SNPs exhibited moderate polymorphism (0.25 < PIC < 0.5; mean PIC = 0.201). The chi-square test results indicated that all nine SNPs were in Hardy-Weinberg equilibrium, with the exception of rs15497877.

Table 4A. Genetic parameters of six SNPs.

SNP ID	A[a]	GFI	GFII	GFIII	AFI	AFII	N_E	PIC	χ^2
rs316142388	CT	0.196	0.489	0.316	0.440	0.560	1.972	0.371	0.025
rs15497877	CT	0.003	0.217	0.780	0.111	0.889	1.246	0.178	3.95
rs314214528	CT	0.296	0.511	0.192	0.552	0.448	1.979	0.372	0.444
rs13553164	CT	0.967	0.033	0.000	0.984	0.016	1.033	0.031	0.111
rs14917305	CT	0.008	0.141	0.851	0.078	0.922	1.168	0.133	0.152
rs13973515	CT	0.886	0.114	0.000	0.943	0.057	1.120	0.102	1.445

A[a] = allele, GF = genotype frequency, AF = allele frequency. GFI, GFII, and GFIII indicate the genotype frequencies of CC, TC, and TT, respectively, and AF1 and AFII indicate the allele frequencies of C and T, respectively. $\chi^2_{0.05}$ (d.f. = 1) = 3.84, $\chi^2_{0.01}$ (d.f. = 1) = 6.64.

Table 4B. Genetic parameters of three SNPs.

SNP ID	A	GFI	GFII	GFIII	AFI	AFII	N_E	PIC	χ^2
rs13972304	AC	0.091	0.460	0.449	0.321	0.679	1.773	0.341	0.606
rs14917647	AC	0.000	0.033	0.967	0.016	0.984	1.033	0.031	0.111
rs13553485	AC	0.477	0.439	0.083	0.697	0.303	1.731	0.333	0.494

A = allele, GF = genotype frequency, AF = allele frequency. GFI, GFII, and GFIII indicate the genotype frequencies of AA, AC, and CC, respectively, and AF1 and AFII indicate the allele frequencies of C and T, respectively. $\chi^2_{0.05}$ (d.f. = 1) = 3.84, $\chi^2_{0.01}$ (d.f. = 1) = 6.64.

Linkage disequilibrium and haplotype analysis

LD analysis results (Table 5) indicated that SNPs rs13553164 and rs13972304 were in complete linkage (D' = 1). SNPs rs13553164, rs14917647, rs14917647, rs13973515, and rs13973515 were in close linkage (D' > 0.99) with rs314214528, rs314214528, rs13972304, rs13553485, and rs13553485, respectively. Moreover, SNPs rs13972304 and rs14917647 were also in linkage (D' > 0.90) with rs314214528 and rs14917305, respectively. The haplotype analysis results (Table 6) showed that 53 haplotypes were successfully established, and 12 of those haplotypes were present at greater than 2.0%. The TTTCCTCAC haplotype accounted for 32.4% of all haplotypes, and CTCCCTCAC and CTCACTCCC haplotypes accounted for 13.9 and 12.8%, respectively.

Table 5. Genetic distance matrix of LD analysis.

SNP	rs15497877	rs314214528	rs13972304	rs13553164	rs14917305	rs14917647	rs13553485	rs13973515
rs316142388	0.371	0.670	0.284	0.506	0.256	0.360	0.333	0.484
rs15497877	-	0.771	0.305	0.212	0.231	0.008	0.210	0.897
rs314214528	-	-	0.977	0.999	0.788	0.993	0.859	0.560
rs13972304	-	-	-	1.000	0.579	0.999	0.632	0.993
rs13553164	-	-	-	-	0.088	0.207	0.153	0.134
rs14917305	-	-	-	-	-	0.911	0.366	0.009
rs14917647	-	-	-	-	-	-	0.174	0.584
rs13553485	-	-	-	-	-	-	-	0.996

Table 6. Results of haplotype analysis.

Haplotype	Sequence	Haplotype frequency
hapl	TTTCCTCAC	0.324
hap2	CTCCCTCAC	0.139
hap3	CTCACTCCC	0.128
hap4	TTCACTCCC	0.061
hap5	CTTCCTCAC	0.059
hap6	TTTCCTCAT	0.034
hap7	TTCACTCAC	0.031
hap8	CTCACTCAC	0.029
hap9	TTCCCTCCC	0.026
hap10	CTCACCCCC	0.024
hap11	CTCCCTCCC	0.023
hap12	TTCCCTCAC	0.021

Bioinformatic analysis of candidate genes

Six candidate genes (Table 7) were obtained and subsequently subjected to Gene Ontology (GO) annotation analyses (Table 8), and the pathways of the candidate genes were analyzed using the KEGG database. The results indicated that the SET domain bifurcated 2 gene (*SETDB2*) was a histone-lysine N-methyltransferase that participated in the lysine degradation pathway (ko00310). The Forkhead box O1 gene (*FOXO1*) participated in the FoxO signaling pathway (ko04068), the transcriptional misregulation in cancer pathway (ko05202), the AMPK signaling pathway (ko04152), the insulin signaling pathway (ko04910), the thyroid hormone signaling pathway (ko04919), and the prostate cancer pathway (ko05215).

Table 7. Allele frequency of five groups and proximal genes.

SNPs	Favorable alleles	Chromosome	Position	Proximal gene
rs316142388	C	1	168504143	*SETDB2*
rs15497877	C	1	168589760	*KPNA3*
rs314214528	C	1	168841831	Unknown
rs13972304	A	1	168931358	Unknown
rs13553164	T	1	169026310	96.808 kb D *DLEU7*
rs14917305	C	1	169093530	29.588 kb D *DLEU7*
rs14917647	A	1	169403027	*INTS6*
rs13553485	C	1	169614824	*ATP7B*
rs13973515	T	1	169868287	8.765 kb D *FOXO1*

Table 8. GO annotation of candidate genes.

Gene name	GO annotation		
	Cellular component	Molecular function	Biological process
SETDB2	Cell nucleus, chromosome	Zinc ion binding, DNA binding	Histone H3-K9 methylation, chromosome segregation
KPNA3	Cytoplasm, nucleus	Protein C-terminus binding, protein transporter activity	Protein import into nucleus
DLEU7	Subcellular entity	Unknown	Unknown
INTS6	Integrator complex, actin cytoskeleton	Unknown	snRNA processing
ATP7B	Trans-Golgi network, perinuclear region of cytoplasm	Copper ion binding	Copper ion export, cellular copper ion homeostasis
FOXO1	Cytoplasm	Protein phosphatase 2A binding, ubiquitin protein ligase binding	Negative regulation of apoptotic, autophagy, gluconeogenesis and protein catabolic process, cellular response to starvation

DISCUSSION

Growth is a very complex trait that is regulated by a number of genes and pathways, and more than 1500 quantitative trait loci have been found to be associated with chicken growth traits (Liu et al., 2008; Uemoto et al., 2009; Wahlberg et al., 2009; Gu et al., 2011). In the present study, 15 previously identified SNPs in *GGA1* were detected using a custom Beadchip analysis. We found that only nine of the 15 SNPs were associated with growth traits in Jinghai yellow chickens, which was not consistent with the previous study. This result might be largely due to the breed difference. Five of the nine SNPs were mainly associated with all of the studied growth traits in our experiment, which indicated that those five SNPs might significantly influence Jinghai yellow chicken growth traits. The accuracy of the GWAS results was affected by the total sample number as well as the number of samples with different genotypes. In the present study, SNPs rs13553164, rs14917647, and rs13973515 were missing genotypes in Jinghai yellow chickens, which might lead to false positives (Cardon and Bell, 2001). Therefore, more samples are needed if further studies are conducted.

N_E and PIC are import group genetic parameters that are used to show the size of intra-population genetic variation (Tao et al., 2008). The results of N_E and PIC analyses showed that five out of the nine SNPs exhibited low polymorphism, while the other four SNPs exhibited moderate polymorphism. The mean of PIC value was 0.210, which was relatively low. Therefore, selection should be continued in order to increase favorable allele frequencies in Jinghai yellow chickens. All of the SNPs were found to be in Hardy-Weinberg equilibrium ($\chi^2 < 3.84$), with the exception of rs15497877, and this might be due to artificial breeding selection.

LD analysis is widely used in genetic parameter calculations, gene mapping, and association studies (Marty et al., 2010). In the present study, two of the nine SNPs were in complete linkage, and the D' values of the other seven SNP pairs were greater than 0.90. Therefore, the 168.5-170.0 Mb region in *GGA1* was in LD. LD is weakened with increased genetic distance between genetic loci (Hosomichi et al., 2008; Abasht et al., 2009). In this study, the general trend indicated that the D' value increased with increased distance between SNPs. However, several SNPs were in linkage with other distant SNPs instead of with close SNPs, which suggested that linkage between SNPs was not only related to distance but was also influenced by other factors such as the recombination rate.

Haplotype analyses for nine SNPs showed that the region was in LD. The frequency of haplotype TTTCCTCAC reached 32.4%, which indicated that this haplotype was important for Jinghai yellow chicken growth traits. According to the results of bioinformatic analyses, we found that most of the candidate genes played important roles in different pathways. The pathway analysis showed that *SETDB2* and *FOXO1* participated in one pathway and six pathways, respectively, and the pathways of the other four genes were unknown but should be further studied. *SETDB2* was mainly studied in zebrafish, and Xu et al. (2010) reported that *SETDB2* possessed potential transcriptional repression activity through catalyzing trimethylation at histone H3 lysine 9 (*H3K9me3*). Moreover, *SETDB2* restricted dorsal organizer formation and regulated left-right asymmetry by suppressing *fgf8a* activity (Xu et al., 2010). Further results indicated that *SETDB2* was also a novel regulator for C&E movements, and it acted by modulating the *dvr1* expression level (Xu et al., 2010; Du et al., 2014). Karyopherin alpha 3 gene (*KPNA3*) belonged to the karyopherin (also known as importin) alpha protein family that functions in the transportation of proteins from the cytoplasm to the nucleus. The alpha karyopherins bind the nuclear localization signals of target proteins for transport from the cytoplasm to the nucleus (Reichelt et al., 1990; Ribbeck et al., 1998).

A previous study demonstrated that SNPs in *KPNA3* were associated with chicken growth traits (Li et al., 2011). Deleted in lymphocytic leukemia 7 gene (*DLEU7*) encodes a protein containing 221 amino acids, and *DLEU7* expression is regulated by the fibroblast growth factor (FGF) pathway during early embryogenesis (Zhu et al., 2012). Moreover, GWAS results showed that the gene was associated with human height (Weedon et al., 2008; Sovio et al., 2009; Kang et al., 2010), which indicated that it might play an important role in chicken growth. *ATP7B* (a member of the P1B-subfamily of the P-type ATPases) plays an important role in normal brain copper homeostasis, which is likely due to the central role that copper plays in a complex network of signaling pathways that regulate several physiological and pathophysiological processes. Therefore, *ATP7B* might significantly influence both physiological and pathophysiological processes (Telianidis et al., 2013). Integrator complex subunit 6 gene (*INTS6*) is a negative regulator of vertebrate organizer gene expression, and it was reported that *INTS6* confined the organizer to dorsal domains, preventing it from extending around the margin into ventral domains (Kapp et al., 2013). Moreover, Xie et al. (2012) reported that a SNP in *INTS6* was significantly associated with body weight at 90 days in F2 chickens. *FOXO1* is a member of the *FOXO* forkhead transcription factors, and it was involved in myogenic growth and differentiation (Leger et al., 2006; Kitamura et al., 2007; Southgate et al., 2007; Yuan et al., 2011), and the overexpression of this gene resulted in weight loss and reduced skeletal muscle mass in both mice and rats (Kamei et al., 2004; Cho et al., 2010). The results of the above studies showed that the six candidate genes, especially *KPNA3, INTS6,* and *FOXO1*, might have significant influence on chicken growth traits.

Conflicts of interest

The authors declare no conflict of interest.

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