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Polymorphisms of *Alu*I and *Hin*1I loci of the *IGF-1R* gene and their genetic effects on growth traits in Bian chickens

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ABSTRACT. Growth traits are important economic traits in broiler chicken production. *Alu*I and *Hin*1I loci are two restriction sites, which are respectively located in exons 2 and 3 of the *IGF-1R* gene. These two loci are significantly related to the growth traits in Jinghai Yellow chickens. In this study, a correlation analysis was performed between these two loci and the growth traits of Bian chickens. The results showed a G376A mutation at the *Alu*I site and a C919A mutation at the *Hin*1I site, which respectively resulted in three genotypes AA, AB, and BB in exon 2 and three genotypes CC, CD, and DD in exon 3. Correlation analysis showed that the female Bian chickens with the AA genotype of the *Alu*I locus had higher body weights than those with the

AB genotype ($P < 0.05$) at 8, 14, 16, and 18 weeks; individuals with CD genotype of *Hin*1I locus had higher body weights at 6, 8, 10, 12, and 14 weeks compared to the CC genotype ($P < 0.05$ or $P < 0.01$). Combined genotypes analysis showed that at the age of 8, 14, 16, and 18 weeks, the body weight of AACC genotype combination was higher than that of the ABCC genotype combination ($P < 0.05$); at the age of 6, 8, 12, 14, 16, and 18 weeks, the AACD genotype combination had higher ($P < 0.05$ or $P < 0.01$) body weight than that of the ABCC genotype.

Key words: Bian chicken; IGF-1R; Growth traits; PCR-RFLP; Marker assisted selection; Broiler breeding

INTRODUCTION

Insulin-like growth factors (IGFs) are one of the most important growth factors in animals. The IGFs family consists of two polypeptide growth factors (IGF-I and IGF-II), two types of receptors (IGF-1R and IGF-2R), and seven binding proteins (IGFBP1-7). The IGFs can promote not only cell growth and development, but also cell differentiation and proliferation (Fan et al., 2005; Arslan et al., 2016). The IGFs are also involved in the metabolism of fat, carbohydrate, and protein (Clemmons D R, 2016). In chickens and other birds, IGF-1R, which is the unique receptor of IGFs (IGF-I and IGF-II), plays a very important role in the function of IGFs and is an important candidate gene affecting the growth and body composition of chickens (Kocamiş and Killefer, 2003; Gao et al., 2009). Growth traits are important economic traits in broiler chicken production and are also important indicators of the production level and economic benefits of farming. The selection of growth traits is essential for broiler breeding. Marker assisted selection (MAS) shortens the process of animal breeding, saves time and money, and becomes the focus of breeding activities (Lu and Wu, 2002).

Single nucleotide polymorphisms (SNPs) in *Alu*I locus of exon 2 and *Hin*1I locus of exon 3 of the *IGF-1R* gene were detected by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) in Bian chickens. The genetic effects of these SNPs on growth traits were also analyzed. The purpose of this study was to identify the correlation markers of growth traits and to provide basic data for MAS.

MATERIAL AND METHODS

Experimental animals

One hundred and eleven F1 female Bian chickens used in this study were randomly obtained from one feeding batch at the Shanxi Livestock and Poultry Breeding Station, Taiyuan, Shanxi, China. We measured body weight of each chicken at different periods. Chicken blood samples were collected from the brachial vein by a standard venipuncture procedure that was approved by the Animal Welfare Committee of Yangzhou University, China. DNA was extracted from the blood samples using the phenol/chloroform method and subsequently diluted to a concentration of 100 μg/μL for later use. We examined the purity of each sample by a spectrophotometer NANO Drop 1000 (Thermo Scientific, Waltham, MA, USA). DNA samples were stored in a freezer at -20°C.

Primer design

Based on the chicken *IGF-1R* gene sequence obtained from the National Center for Biotechnology Information (NCBI) GenBank database (Reference Sequence: NC_006097.4), the Primer Premier 5.0 software was used to design two pairs of primers (Table 1). The primers were commercially synthesized by Sangon Biotech (Shanghai, China).

Table 1. Primers used in the study.

Primer	Sequence (5'→3')	Fragment size (bp)	Location	Annealing temperature (°C)
*Alu*I	F: AACGCCTGGAGAACTGTACG R: ATCGCTGAGGCTTTCCAAG	155	Exon 2	56
*Hin*1I	F: GAGCCTGCACAGACCAGAAT R: CAGGGACTTTGGAGCAGAAC	195	Exon 3	58

PCR amplification

PCR was performed in a 20-μL reaction mixture containing 1 μL chicken genomic DNA (100 μg/μL); 2 μL 10X buffer; 2.2 μL $MgCl_2$ (25 mM); 0.8 μL dNTPs (10 mM); 1 μL forward primer (10 μM); 1 μL reverse primer (10 μM); 0.2 μL of Taq DNA polymerase (5 U/μL); and 11.8 μL ddH_2O. The amplification conditions were: denaturation at 94°C for 5 min; followed by 30 cycles of denaturation at 94°C for 30 s, annealing at the primer-specific temperatures (Table 1) for 30 s, and extension at 72°C for 35 s, as well as a final elongation step at 72°C for 10 min.

PCR-RFLP and sequencing

PCR products were digested with restriction enzymes *Alu*I and *Hin*1I at 37°C for 2 h in a 20-μL reaction mixture containing 1 μL DNA products, 16.5 μL ddH_2O, 2 μL 10X buffer, and 0.5 μL appropriate restriction enzyme (10u/μL). The digested products were verified by 10% non-denaturing polyacrylamide gel electrophoresis at 200 V for 5 h, and then the gels were visualized by silver staining. The homozygous PCR amplification products were sent to Sangon Biotech (Shanghai) for direct two-way sequencing.

Statistical analysis

General linear models (GLMs) were established to analyze the genotype effects of the *IGF-1R* gene on growth traits. All statistical procedures were performed using the statistical software SPSS13.0. The following two linear models were used for the least-squares analysis of growth traits:

$$Y_{ij} = \mu + G_i + e_{ij} \quad \text{(Equation 1)}$$

$$Y_{ijk} = \mu + G_i + G_j + G_{ij} + e_{ijk} \quad \text{(Equation 2)}$$

where, Y is the growth trait; μ is the overall mean; G is the genotype effect of the *IGF-1R* gene; G_{ij} is the interaction effect of the two loci, and e is the random error (Li et al., 2012; Zhang et al., 2012; Huang et al., 2013).

RESULTS

Electrophoresis of PCR products

The lengths of the product fragments amplified by specific primers were consistent with those of the amplified fragments, and no non-specific amplification products were detected. PCR-RFLP detection can be carried out.

PCR-RFLP and sequencing

We detected two mutations separately located at base pair positions 16719640 and 16939213 on chromosome 10 of the chicken. They were also separately located at base pair position 376 in exon 2 and 919 in exon 3 of the *IGF-IR* gene in Bian chickens. Three genotypes AA, AB, and BB (Figure 1) were detected when the amplification products were digested by the *Alu*I enzyme. The direct sequencing results of the two homozygous genotypes AA and BB are shown in Figure 2. A mutation site G376A was detected by sequence comparison. When a guanine (G) is located at position 376, two fragments of 90 and 65 bp were detected; when an adenine (A) is located at position 376, the *Alu*I restriction site cannot be detected (Figure 2).

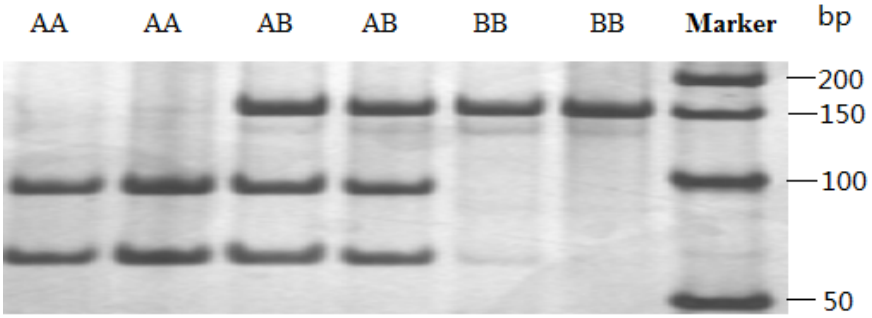

Figure 1. Results of *Alu*I enzyme digestion. AA genotype, AB genotype, BB genotype.

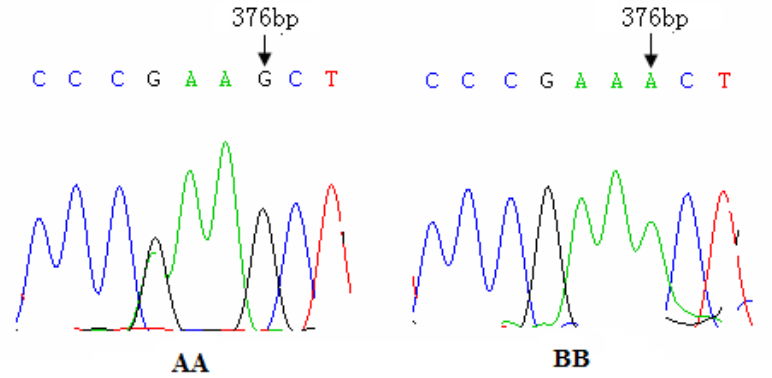

Figure 2. Sequence maps for the genotypes of AA and BB.

Three genotypes CC, CD, and DD (Figure 3) were detected, when the amplification products were digested by the *Hin*1I enzyme. Sequencing results of the two homozygous genotypes CC and DD are shown in Figure 4. A mutation site C919A was detected by sequence comparison. When a cytosine (C) is located at position 919, two fragments of 110 and 85 bp were detected; when an adenine (A) is located at position 919, the *Hin*1I restriction site cannot be detected (Figure 4).

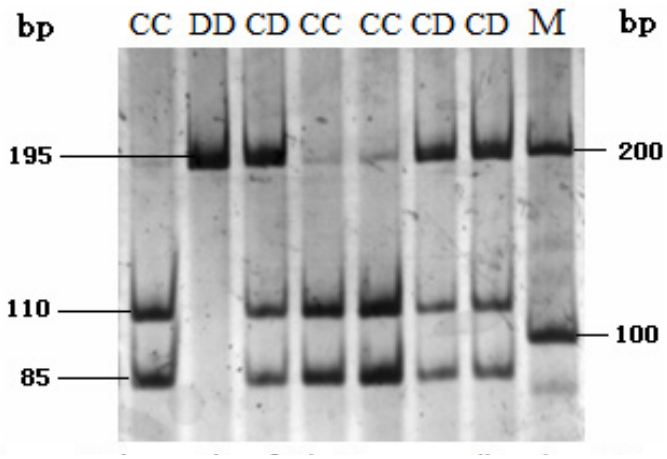

Figure 3. Results of *Hin*1I enzyme digestion. CC genotype, DD genotype and CD genotype.

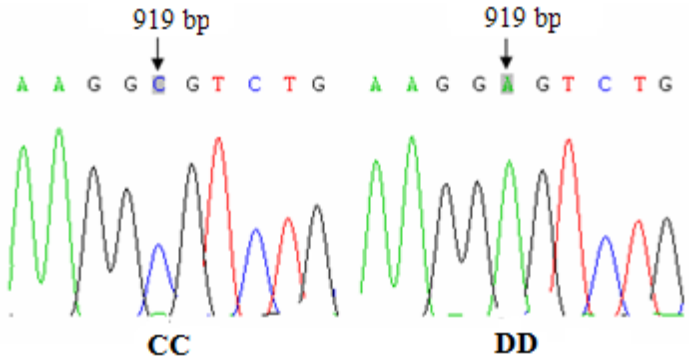

Figure 4. Sequence maps for the two genotypes of CC and DD.

Genotype and allele frequencies

Genotype and allele frequencies of *Alu*I and *Hin*1I loci are presented in Table 2. The genotype frequencies of AA, AB, and BB were 0.685, 0.297, and 0.018, respectively. Therefore, the allele A was the major allele in the population (0.833). The results of Chi-test showed that the *Alu*I locus of *IGF-1R* was in Hardy-Weinberg equilibrium ($P > 0.05$) in Bian chickens. The genotype frequencies of CC, CD, and DD were 0.568, 0.414, and 0.018, respectively. Therefore, the allele C was the major allele in the population (0.775). The

results of Chi-test showed that the *Hin*1I locus in the Bian chicken *IGF-1R* was not in Hardy-Weinberg equilibrium ($P < 0.05$). This might have resulted from the selection, mutation, or migration and sample size.

Table 2. Genotypes and allele frequencies at *Alu*I and *Hin*1I sites of the *IGF-1R* gene.

Breed	Number	Genotypes frequencies			Allele frequency		χ^2
Bian chicken	111	AA	AB	BB	A	B	
		0.685 (76)	0.297 (33)	0.018 (2)	0.833	0.167	0.55
	111	CC	CD	DD	C	D	
		0.568 (63)	0.414 (46)	0.018 (2)	0.775	0.225	3.90

Numbers in parentheses indicate the number of individuals; $\chi^2_{0.05}$ (d.f. = 1) = 3.84.

Association of the *IGF-1R* gene with growth traits

The least squares means between the growth traits and different genotypes of the *Alu*I locus in Bian chickens are presented in Table 3. The female Bian chickens of the genotype AA had a higher body weight than those of the genotype AB ($P < 0.05$) at 8, 14, 16, and 18 weeks of age. The least squares means between the growth traits and different genotypes of *Hin*1I locus in Bian chickens are presented in Table 4. The significant differences ($P < 0.05$ or $P < 0.01$) between the genotypes CD and CC were found at 6, 10, 8, 12, and 14 weeks of age. Genotype combination analysis (Table 5) showed that at the age of 8, 14, 16, and 18 weeks, the body weight of the AACC genotype combination was higher than that of the ABCC genotype combination ($P < 0.05$); at the age of 6, 8, 12, 14, 16, and 18 weeks, the AACD genotype combination had a significantly higher ($P < 0.05$ or $P < 0.01$) body weight than that of the ABCC genotype combination.

Table 3. Association analysis between the *Alu*I site and growth traits.

Traits	Genotypes			SIG
	AA (76)	AB (33)	BB (2)	
Body weight at birth (g)	35.87 ± 0.46	35.61 ± 0.66	35.00 ± 1.00	NS
Body weight at 6 weeks (g)	432.37 ± 6.12	417.73 ± 11.95	389.50 ± 57.50	NS
Body weight at 8 weeks (g)	597.36 ± 8.10^{a}	569.09 ± 12.70^{b}	544.50 ± 60.50^{ab}	*
Body weight at 10 weeks (g)	765.68 ± 10.77	747.15 ± 17.19	701.00 ± 93.00	NS
Body weight at 12 weeks (g)	930.36 ± 13.66	891.88 ± 20.40	888.00 ± 122.00	NS
Body weight at 14 weeks (g)	1101.36 ± 15.97^{a}	1047.67 ± 26.10^{b}	1003.00 ± 151.00^{ab}	*
Body weight at 16 weeks (g)	1216.08 ± 18.25^{a}	1152.85 ± 28.92^{b}	1091.00 ± 169.00^{ab}	*
Body weight at 18 weeks (g)	1307.68 ± 20.29^{a}	1238.91 ± 31.41^{b}	1235.50 ± 147.50^{ab}	*

Means in the same row with different superscripts differ significantly; SIG = significance; *significant ($P < 0.05$); NS = not significant; the numbers within parentheses refer to genotype numbers.

Table 4. Association analysis between the *Hin*1I site and growth traits.

Traits	Genotypes			SIG
	CC (63)	CD (46)	DD (2)	
Body weight at birth (g)	36.015 ± 0.43	35.57 ± 0.66	33.00 ± 1.00	NS
Body weight at 6 weeks (g)	417.40 ± 8.15^{b}	442.15 ± 6.98^{a}	394.50 ± 5.00^{ab}	*
Body weight at 8 weeks (g)	572.19 ± 9.86^{B}	610.25 ± 8.63^{A}	565.00 ± 2.00^{AB}	**
Body weight at 10 weeks (g)	744.59 ± 13.03^{b}	777.24 ± 12.18^{a}	718.00 ± 23.00^{ab}	*
Body weight at 12 weeks (g)	901.97 ± 16.76^{b}	942.09 ± 14.32^{a}	877.50 ± 16.50^{ab}	*
Body weight at 14 weeks (g)	1063.03 ± 20.08^{b}	1113.96 ± 17.71^{a}	1034.50 ± 6.50^{ab}	*
Body weight at 16 weeks (g)	1177.67 ± 22.70	1221.20 ± 20.66	1140.00 ± 1.00	NS
Body weight at 18 weeks (g)	1267.00 ± 24.05	1313.52 ± 24.32	1248.00 ± 25.00	NS

Means in the same row with different superscripts differ significantly; SIG = significance; *significant ($P < 0.05$); **significant ($P < 0.01$); NS = not significant; the numbers within parentheses refer to genotype numbers.

Table 5. Association analysis between the combination genotypes and growth traits.

Traits	Genotypes				SIG
	AACC (34)	ABCC (28)	AACD (40)	ABCD (5)	
Body weight at birth (g)	36.09 ± 0.53	35.93 ± 0.72	35.83 ± 0.74	33.80 ± 1.46	NS
Body weight at 6 weeks (g)	424.15 ± 10.30^{ab}	412.25 ± 13.16^{b}	441.25 ± 7.44^{a}	448.40 ± 26.71^{ab}	*
Body weight at 8 weeks (g)	587.21 ± 14.46^{ABa}	557.11 ± 12.77^{Bb}	607.60 ± 9.12^{Aa}	636.20 ± 32.15^{ABa}	**
Body weight at 10 weeks (g)	756.62 ± 18.48^{ab}	734.86 ± 18.33^{b}	771.98 ± 13.10^{ab}	816.00 ± 38.89^{a}	*
Body weight at 12 weeks (g)	925.65 ± 24.71^{ab}	878.07 ± 21.80^{b}	937.00 ± 15.40^{a}	969.20 ± 47.55^{ab}	*
Body weight at 14 weeks (g)	1094.44 ± 28.58^{a}	1032.43 ± 27.08^{b}	1110.58 ± 18.31^{a}	1133.00 ± 78.10^{ab}	*
Body weight at 16 weeks (g)	1214.68 ± 32.40^{a}	1141.86 ± 30.15^{b}	1221.08 ± 21.31^{a}	1214.40 ± 93.17^{ab}	*
Body weight at 18 weeks (g)	1305.24 ± 34.40^{a}	1226.96 ± 32.64^{b}	1312.75 ± 25.43^{a}	1305.80 ± 102.59^{ab}	*

Means in the same row with different superscripts differ significantly; SIG = significance; *significant ($P < 0.05$); **significant ($P < 0.01$); NS = not significant; the numbers within parenthesis refer to genotype numbers.

DISCUSSION

Polymorphisms of the *IGF-1R* gene

Some studies of the *IGF-1R* gene have been reported. A total of 11 novel polymorphisms of the *IGF-1R* gene were detected in the Egyptian water buffalo by El-Magd et al. (2013). Moe et al. (2007) specified the existence of 21 SNPs by sequence comparison of the IGF1R coding region between LL and SS birds. Three SNPs (G26333A, G263336A, and C26639T) were detected in exon 2 of *IGF-1R* in Jinghai Yellow chickens by Yang et al. (2012). Each of the SNPs resulted in three genotypes and all loci were in Hardy-Weinberg equilibrium ($P > 0.05$).

In the present study, we detected two mutations located in exons 2 and 3 of the *IGF-1R* gene, respectively. The mutation G376A in exon 2 resulted in the generation of three genotypes AA, AB, and BB. The other mutation C919A in exon 3 also resulted in the generation of three genotypes CC, CD, and DD. The genotype frequencies of CC, CD, and DD were 0.568, 0.414 and 0.018, respectively.

Correlation analysis between *IGF-1R* gene and growth traits

IGF-1R is the main receptor of IGF1 and IGF2, and it plays an important role in the regulation of the muscle development, metabolism, and growth in mammals (Delafontaine et al., 2004; Xing et al., 2007). Several studies on the *IGF-1R* gene have been reported in mammals (Kawashima et al., 2005; Proskura and Szewczuk, 2014; Szewczuk, 2016). When Lei et al. (2008) studied the associations of the *IGF-1R* gene with chicken early growth and carcass traits in the Xinghua and White Recessive Rock chickens, they found that six SNPs (C17445985T, G17445596A, A17307750G, A17307494G, A17299834G, and C17293932T) were possibly associated with growth traits. Analysis of the genetic polymorphisms of exons 4 and 13 of the *IGF-1R* gene by Gao et al. (2009) showed two mutation sites C919G and T2761C. The C919G locus had a significant impact on the body weight at five weeks ($P < 0.05$), and the T2761C locus had a certain effect on the body weight at seven weeks ($P < 0.1$). Furthermore, Jin et al. (2012) studied the same sites in Jinghai Yellow chickens as we studied in Bian chickens. The results of the *Alu*I site showed that the BB genotype had a higher body weight than the AA genotype at the age of eight weeks ($P < 0.05$), and the body weight of BB genotype was higher than that of the AA and AB genotypes at the age of 12 weeks ($P < 0.05$). The results of the *Hin*1I site showed that the body weight of the DD genotype was higher than that of the CC and CD genotypes at birth, and the DD genotype had a higher body weight than the CC genotype at the age of 300 days ($P < 0.05$).

Our results showed that the homozygous genotype AA at *Alu*I site and the heterozygous genotype CD at *Hin*1I site were beneficial for the weight gain of Bian chickens; this was not consistent with the results obtained by Jin et al. (2012) in Jinghai Yellow chickens. The difference in results might be due to the difference in the breed of chickens studied. Analysis through software DNAman, version 5.2.2 (Lynnon BioSoft, USA) showed that neither of the two mutations (G376A and C919A) caused the change of amino acid. However, both mutations have significant effects on the growth traits of Bian chickens. There might be some cis-acting elements around the mutation site. A change of nucleotide might lead to a change in the function of the elements. Thus, it could affect the expression of the *IGF-1R* gene, and finally have an impact on the growth traits. In the whole period of the growth, the body weights of different genotypes have such regularities: AA>AB>BB, CD>CC>DD (except for the weight at birth). Allele A was a weight enhancer gene and allele B was a leaky one. The genotype CD showed obvious heterosis in weight gain.

The combination of the two loci of *IGF-1R* resulted in a total of seven genotype combinations: AACC, ABCC, AACD, ABCD, AADD, CCBB, and BBCD. Because the individuals of AADD, BBCC, and BBCD genotype combinations were too few to be representative, it was not necessary to analyze their correlations with growth traits. At 6, 8, 10, 12, and 14 weeks, the individuals of ABCD genotype combination showed the highest body weight. The individuals of AACD genotype combination showed the highest weight at 16 and 18 weeks.

On the basis of the above findings, the *Alu*I locus in exon 2 and the *Hin*1I locus in exon 3 of the *IGF-1R* gene had significant effects on the growth traits of Bian chickens. Our study provides the basic information for the MAS of Bian chickens.

CONCLUSION

In the present study, two mutations were detected in the *IGF-1R* gene of Bian chickens. The mutation G376A at *Alu*I site in exon 2 of the *IGF-1R* gene resulted in three genotypes AA, AB, and BB. The other mutation C919A at *Hin*1I site in exon 3 of the *IGF-1R* gene resulted in three genotypes CC, CD, DD. Correlation analysis showed that the *Alu*I site had a significant effect on the body weights at 8, 14, 16 and 18 weeks ($P < 0.05$); a significant difference ($P < 0.05$ or $P < 0.01$) was observed between the *Hin*1I locus and body weights at 6, 8, 10, 12, and 14 weeks. The genotype combinations of the two loci had significant effects on the body weights in all weeks, except for the birth weight.

Conflicts of interest

The authors declare no conflict of interest.

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