



A New Single Nucleotide Polymorphism in the IGF-I Gene and Its Association with Growth Traits in the Nanjiang Huang Goat*

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ABSTRACT : The objectives of this study were to identify polymorphisms of insulin-like growth factor I (IGF-I) gene and to investigate their association with growth traits in Nanjiang Huang goats. Five hundred and ninety-two animals were used to detect the polymorphisms in the complete coding sequence, part of introns and the 5'-regulatory region of the *IGF-I* gene by means of PCR-SSCP. A new single nucleotide polymorphism (G to C transversion) was identified at intron 4 of the *IGF-I* gene in the goats. Two alleles and three genotypes were observed in this group. The frequency of G and C alleles was 54.6 and 45.4%, respectively. The statistical analysis showed that polymorphism of the *IGF-I* gene had a significant association ($p < 0.05$) with birth weight (BW), body weight at 6 months (W6) and at 12 months (W12), heart girth at 2 months (G2), body length at 6 months (L6), wither height at 6 months (H6) and at 12 months (H12) and heart girth at 12 months (G12). The goats with genotype CC had significantly higher BW, W6, W12, G2, L6, H6, H12 and G12 than those with genotype GC and had significantly higher W12, H6, H12 and G12 than those with genotype GG. Therefore, genotype CC may be the most advantageous for growth traits in the Nanjiang Huang goat. However, no significant association between SNP genotypes and other growth traits was observed. These results indicated that the SNP marker of the *IGF-I* gene may be a potential molecular marker for growth traits in Nanjiang Huang goats. (**Key Words :** Nanjiang Huang Goats, Insulin-like Growth Factor I, Polymorphism, Growth Traits, PCR-SSCP)

INTRODUCTION

The Nanjiang Huang goat, as a meat breed, is known to have relatively high growth rate and high reproduction rate in extensive systems in the mountain areas of South China, compared with other Chinese native goats. For the past forty years, genetic improvement has been achieved by selection based on phenotype information, but this breed still presents a wide spectrum of variability in growth rate and reproduction rate (Zhang et al., 2005). It is very difficult to make rapid genetic improvement if using traditional methods of selection within breed. However, the genetic improvement of polygenic traits, like growth and meat production, can be enhanced by marker assisted selection which has higher accuracy in estimating the genetic value of animals (Dekker, 2004).

Genetic markers associated with traits of interest can be searched directly by applying molecular biology techniques, which can identify genetic variation at specific loci and analyze the relationship between genetic variation at quantitative trait loci (QTL) and production traits (Jiang et al., 2002; Arora and Bhatia, 2006; Missouhou et al., 2006). Candidate gene strategy, a main approach, is used to identify genetic variation at genes affecting the physiological pathways related to a phenotype, which would be more likely to affect the quantitative variation in that phenotype than genes or chromosome regions chosen by chance (Schwerin et al., 1995; Lan et al., 2007).

Growth is a complex process that involves the regulated coordination of a wide diversity of neuroendocrine pathways. Among these pathways, the somatotrophic axis (GH/IGF-I axis) should be emphasized because of its key roles in postnatal growth and metabolism in mammals (Shoshana et al., 2000; Burkhard et al., 2005). As an important component of the somatotrophic axis, insulin-like growth factor I (IGF-I) is believed to stimulate anabolic process such as cell proliferation, skeletal growth and protein synthesis (Froesch et al., 1985; Baxker et al., 1986; Clemmons et al., 1987). IGF-I null mutant mice exhibit a

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Table 1. Primer sequences, amplified region and fragment size for PCR amplification of goat *IGF-I* gene

Amplified region	Primer sequence ^c (5'-3')	GenBank accession No.	Fragment size and location (bp)	Annealing temperature (°C)
Promoter ^a	ccaggttctaggaaatga	AF017143	311	55.6
P	gacaagaggagcagaca		1-311	
Exon 1 ^b	ccccagctgttctctgtcta	D26116	354	56.9
(E1)	gaaaattccccaatgacttcaa		1,886-2,240	
Exon 1a ^b	accacaaagcagcacat	D26116	144	53.5
(E1a)	agggaacagtcataagaaa		3,914-4,057	
Exon 3 ^b	caaggaccagaggaagat	D26117	282	55.6
(E3)	cagccacaggcagtcattc		378-660	
Exon 4 ^b	gctgggtgtagcagtgaaca	D26118	320	55.6
(E4)	gttgcttcagccgcataact		308-627	
Exon 6 ^b	aggttgagatccagtgttag	D26119	210	61.5
(E6)	taactcgtgcagagcgaagg		44-253	

^a The primers of the regulatory region of the *IGF-I* gene were designed according to the published nucleotide sequence by Ge et al. (1997), who reported a SNP (T to C transition) in this region.

^b Primers were designed according to the published nucleotide sequence information of the goat *IGF-I* gene.

^c Primer pairs were designed using Primer 5.0 (PREMIER Biosoft International, Palo Alto, CA, USA) and synthesized by Shanghai Bioasia Biotechnology Co. Ltd. in China.

lower skeletal growth rate compared with their wild-type littermates (Baker et al., 1993). Therefore, the gene encoding IGF-I is viewed as a promising candidate gene for marker-assisted selection of growth traits. In the goat, the *IGF-I* gene is encoded by a single gene located on chromosome 5 (Schibler et al., 1998), consisting of three leader exons (1w, 1 and 1a) and three exons (3, 4 and 6), in which exon 3 and exon 4 encode the mature IGF-I peptide (Mikawa et al., 1995). Several genetic polymorphisms of the *IGF-I* gene associated with growth traits have been reported in the chicken (Seo et al., 2001; Amills et al., 2003; Zhou et al., 2005; Bennett et al., 2006), in swine (Casas et al., 1997), and in the bovine (Ge et al., 2001; Li et al., 2004; Chung and Kim, 2005; Crui et al., 2005a, b). However, there are few reports on polymorphisms of the goat *IGF-I* gene. Thus, the aims of the present study were to identify polymorphisms of the *IGF-I* gene and to investigate association of these polymorphisms with growth traits in the Nanjiang Huang goat.

MATERIALS AND METHODS

Animals and phenotypic data

Blood samples of 592 goats (492 females and 100 males) were collected from twelve half-sib families in four groups at the Breeding Institute of Nanjiang Huang Goat, in Nanjiang county, Sichuan province, South China. The animals were grazed extensively on mountain pasture all year around with similar rearing and feeding conditions. Mating periods started on September 15 every year and continued for 12 weeks. Mating was performed by artificial insemination. Kids were weaned at the age of 2 months.

All data were collected from the Breeding Institute records during the period of 1997 to 2003. The data included the identification of the animal, its sire, year of

birth, sex, litter size, body weights including birth weight (BW), body weight at 2 months (W2), at 6 months (W6) and at 12 months (W12); body measurements including body length at 2 months (L2), at 6 months (L6) and at 12 months (L12), wither height at 2 months (H2), at 6 months (H6) and at 12 months (H12) and heart girth at 2 months (G2), at 6 months (G6) and at 12 months (G12). Body weight was obtained by actual weighing with an electronic scale for BW and a scale for W2, W6 and W12, which was the average of two weighings taken on two consecutive days in the morning before grazing. After weighing, the body measurements were taken from the right side of each animal by two people using metal tape and averaged.

DNA isolation and PCR amplification

Genomic DNA was isolated using the phenol-chloroform extraction technique and diluted to 50 ng/μl for PCR amplification. The 5'-regulatory region and five exons of the *IGF-I* gene were amplified by PCR using six primer pairs shown in Table 1. The PCR reactions were performed in a total volume of 15 μl containing 50 ng genomic DNA, 44 pmol of each primer, 0.2 mmol of dNTP, 0.75 U *Taq* DNA polymerase (Dingguo Biotechnology Company, Beijing, China) and 1.5 μl 10×PCR buffer (200 mmol Tris-HCl, 100 mmol (NH₄)₂SO₄, 100 mmol KCl, 1% Triton X-100, 20 mmol MgCl₂, pH 8.8) in a PTC-200 Peltier Thermal Cycler (MJ Research Inc, Hercules, CA, USA). Samples were initially denatured at 94°C for 5 min, followed by 34 cycles of 94°C for 30 s, 53.5°C-61.5°C (Table 1) for 30 s, 72°C for 30 s, and a final extension at 72°C for 10 min.

Genotyping and sequencing

The PCR products were genotyped by single stranded

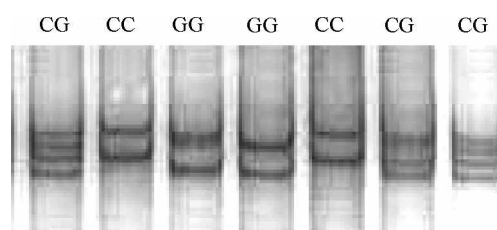


Figure 1. Genotypes of SSCP analysis of the E4 sequence in goat *IGF-I* gene.

conformational polymorphism (SSCP). Two microlitres of each PCR product was added to 8 µl of denaturing buffer (98% formamide, 10 mmol EDTA, 0.05% xylene cyanol and 0.05% bromophenol blue). The mixtures were denatured at 95°C for 10 min, rapidly chilled in ice for 5 min, and then loaded onto 12% polyacrylamide/TBE gels (49:1 acrylamide to bis-acrylamide) for products of primers P, E1, E3, E4 and 12% polyacrylamide/TBE gels (29:1 acrylamide to bis-acrylamide) for products of primers E1a and E6, and electrophoresed at 120 V for 6 h at room temperature (Jia et al., 2005; Liu et al., 2007). After the electrophoresis, the gel was removed from the apparatus and stained with silver nitrate to visualize the banding patterns.

The PCR products of the different homozygous individuals were purified using the DNA Fragment Quick purification Kit (Tianwei, Biotechnology, Company, Beijing, China), and cloned into pGEM-T Easy Vector Kit (Promega, Madison, WI, USA), then sequenced using a 3730 sequencer (Applied Biosystems 3730xl DNA Analyzer).

Statistical analysis

Allele frequencies were estimated by the gene-counting method and genotype distribution of the polymorphisms was tested for Hardy-Weinberg equilibrium by chi-square analysis.

Association between polymorphisms of the *IGF-I* gene and growth traits was analyzed using the general linear model (version 8.2; SAS Institute Inc., Cary, NC, USA). The linear model (Model 1) for BW, L2, H2 and G2 was as

follow:

$$Y_{ijkl} = \mu + G_i + YS_j + S_m + L_n + F_k + Q_l + e_{ijkl} \quad (\text{Model 1})$$

where Y_{ijkl} is an observation of dependent variable (BW, L2, H2 and G2); μ is the overall mean for each trait; G_i is the effect of i_{th} *IGF-I* genotype ($k = GG, GC, CC$); YS_j is the effect of j_{th} year ($j = 1-6$); S_m is the effect of m_{th} sex ($m = 1, 2$); L_n is the effect of n_{th} litter size ($n = 1, 2, 3$); F_k is the effect of k_{th} sire ($k = 1-12$); Q_l is the effect of l_{th} group ($l = 1-4$) and e_{ijkl} is the random error.

For association between polymorphisms of the *IGF-I* gene and W2, W6 and W12, analysis of covariance was performed with BW as a covariate to eliminate the effect of significant difference in BW. Analysis of covariance was also performed for association of different genotypes with L6 and L12, H6 and H12, G6 and G12 with L2, H2, and G2, respectively, as a covariate. Model 2 for covariance analysis was as follow:

$$Y_{ijkl} = \mu_y + G_i + YS_j + S_m + L_n + F_k + Q_l + \beta(x_{ijkl} - \mu_x) + e_{ijkl} \quad (\text{Model 2})$$

Where, Y_{ijkl} is an observation of dependent variable (W2, W6, W12, L6, H6, L12, H12 and G12); x_{ijkl} is an observation of covariate (BW, L2, H2 and G2, respectively); β is the regression coefficient with which Y_{ijkl} has a linear regression on x_{ijkl} ; μ_y is the overall mean for each trait; μ_x is the overall mean for each covariate; G_i , YS_j , S_m , L_n , F_k , Q_l and e_{ijkl} stand for the same effect as in Model 1.

RESULTS

SSCP polymorphisms and sequences analysis

Six fragments, amplified by PCR using the primers described in Table 1, showed the expected lengths. The polymorphisms of the PCR products in all individuals were analyzed by PCR-SSCP. However, only the products of primers E4 exhibited polymorphism. The homozygotes

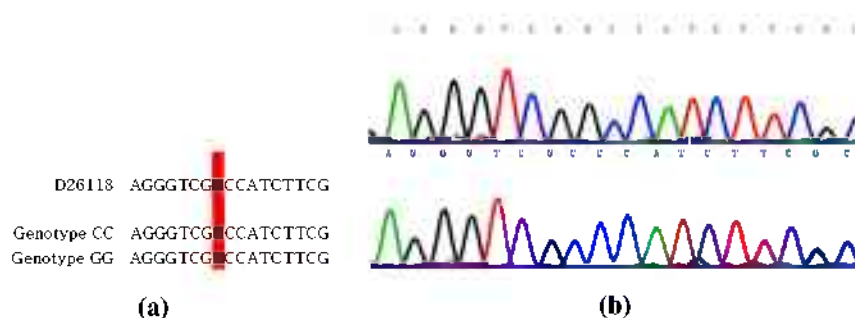


Figure 2. Nucleotide sequence comparison of the PCR products of primers E4; (a) BLAST results of the nt sequence of genotype GG and CC in this study with previously published nt sequence in GenBank; (b) nt sequence of genotype GG and CC (the arrow pointed to the mutation site).

exhibited two distinct bands with altered mobility, whereas the heterozygotes showed four bands (Figure 1). Sequence analysis revealed a point mutation at position 589 of the sequence with accession number D26118, which was not located at the encoding sequence of exon 4 of the *IGF-I* gene (from 376 bp to 557 bp), but located at intron 4 of the *IGF-I* gene (from 558 bp to 608 bp). A nucleotide transversion from Guanine (G) to Cytosine (C) was found (Figure 2). The C allele was defined as the nucleotide sequence with the G→C mutation, and the G allele as the sequence without this mutation.

Genotype and allele frequencies

The allele and genotype frequencies of the *IGF-I* gene in Nanjiang Huang goats are shown in Table 2. The genotype frequency was 35.8, 37.5 and 26.7% for GG, GC and CC, respectively. The allele frequency for G and C was 54.6% and 45.4%, respectively. This locus displayed a larger number of individuals with GG and CC genotypes than the values expected from the Hardy-Weinberg

principle.

Association analysis

The results of association analysis are given in Table 3 for body weights and in Table 4 for body measurements. In the analysis of 592 Nanjiang Huang goats, the *IGF-I* gene polymorphism was associated with BW ($p < 0.0001$). Goats with genotype CC had higher BW than those with genotype GG and GC ($p < 0.05$). After adjusting for BW, significant association between the *IGF-I* gene polymorphism and W6 ($p = 0.0023$) and W12 ($p = 0.0002$) was observed. Goats with genotype CC had 1.17 kg higher W6 than those with genotype GC ($p < 0.05$). Animals with genotype CC and GG had 2.04 kg and 1.03 kg higher W12 than those with genotype GC, respectively. Goats with genotype CC had 1.01 kg higher W12 than genotype GG ($p < 0.05$). However, there were no significant effects of *IGF-I* genotypes on W2 ($p > 0.05$).

Significant association between polymorphism of the *IGF-I* gene and G2 was observed ($p = 0.0192$). Goats with

Table 2. Genotype and allele frequencies of the *IGF-I* gene in Nanjiang Huang goats

Traits	Genotypes			Allele		χ^2
	GG	GC	CC	G	C	
No.	212	222	158			35.17**
Frequencies (%)	35.8	37.5	26.7	54.6	45.4	

** $p < 0.01$.

Table 3. Association between the *IGF-I* genotypes and body weights in Nanjiang Huang goats

Traits ¹	Genotypes (LSM±SE)			f-value	p-value
	GG	GC	CC		
BW	2.22±0.06 ^b	2.26±0.05 ^b	2.39±0.06 ^a	12.82	<0.0001
W2 ²	9.62±0.20	9.63±0.20	9.81±0.21	1.54	0.2156
W6 ²	19.17±0.61 ^{ab}	18.76±0.58 ^b	19.93±0.63 ^a	6.15	0.0023
W12 ²	29.18±0.88 ^b	28.15±0.85 ^c	30.19±0.81 ^a	8.49	0.0002

In the same row, values with different superscripts are significantly different ($p < 0.05$).

¹ BW: birth weight; W2: body weight at 2 months; W6: body weight at 6 months; W12: body weight at 12 months.

² The least square means of W2, W6 and W12 were adjusted for BW.

Table 4. Association between the *IGF-I* genotypes and body measurements in Nanjiang Huang goats

Traits ¹	Genotypes (LSM±SE)			f-value	p-value
	GG	GC	CC		
L2	44.70±0.61	44.56±0.58	45.62±0.63	2.12	0.1214
H2	42.37±0.54	42.65±0.53	42.92±0.74	2.22	0.1095
G2	48.36±0.74 ^{ab}	47.58±0.72 ^b	49.33±0.77 ^a	4.66	0.0129
L6 ²	57.26±0.61 ^{ab}	57.00±0.59 ^b	58.00±0.62 ^a	4.55	0.0110
H6 ²	54.17±0.55 ^b	53.92±0.54 ^b	54.84±0.57 ^a	4.48	0.0117
G6 ²	63.59±0.75	63.33±0.73	64.02±0.77	1.41	0.2455
L12 ²	65.53±0.73	65.21±0.70	66.08±0.75	2.30	0.1011
H12 ²	62.11±0.68 ^b	61.88±0.67 ^b	62.93±0.70 ^a	3.99	0.0190
G12 ²	71.62±0.83 ^b	71.58±0.80 ^b	72.87±0.85 ^a	4.61	0.0104

In the same row, values with different superscripts are significantly different ($p < 0.05$).

¹ L2: body length at 2 months; H2: wither height at 2 months; G2: heart girth at 2 months; L6: body length at 6 months; H6: wither height at 6 months; G6: heart girth at 6 months; L12: body length at 12 months; H12: wither height at 12 months; G12: heart girth at 12 months.

² The least square means of L6 and L12 were adjusted for L2, the least square means of H6 and H12 were adjusted for H2; the least square means of G6 and G12 were adjusted for G2.

A new SNP (G to C conversion) was detected at intron 4 of the *IGF-I* gene in the present study. Three genotypes and two alleles were identified by SSCP in the *IGF-I* gene (Figure 1). The distribution of allele and genotype frequencies in our sample significantly deviated from the

Hardy-Weinberg equilibrium ($\chi^2 = 35.17$, $p < 0.01$), indicating that the locus is under selection pressure. The differences between genotypes and alleles are possibly due to long-term artificial fertilization and selection towards high growth rate.

The current results demonstrated that the CC genotype was associated with higher BW, W6 and W12 in Nanjiang Huang goats (Table 3). The goats with genotype CC had over 7.7% and 5.8% higher BW than those with genotype GG and genotype GC, respectively. The animals with genotype CC had the larger W6 and W12 in the population, respectively higher by 1.17 kg and 2.04 kg, than those with genotype GC, and had 1.01 kg higher W12 than those with genotype GG. This result demonstrated a dominance effect of the C allele over the G allele on BW, W6 and W12, indicating that animals with genotype CC have the higher growth rate after weaning. This is in line with the report that heritability for mean serum IGF-I concentration is high (0.48) during the postweaning period in Angus cattle (Davis and Simmen, 1997). Therefore, further studies are needed to investigate the relation of the different genotypes with circulating IGF-I concentration in Nanjiang Huang goats and other breeds.

In our study, significant association between genotypes and G2, L6, H6, H12 and G12 were observed in Nanjiang Huang goats (Table 4). The goats with the CC genotype were 1.76 cm, 1.00 cm, 0.92 cm, 1.05 cm and 1.29 cm higher than those with the GC genotype in G2, L6, H6, H12 and G12, respectively. Animals with the CC genotype were 0.67 cm, 0.82 cm and 1.24 cm higher than those with the GG genotype in H6, H12 and G12, respectively. For animals with genotype CC, the significant increase in W6 resulted from the significant increase in L6 and H6, and the significant increase in W12 resulted from the significant increase in H12 and G12. These results indicated that goats with genotype CC had higher weight and larger body size than other genotypes. Therefore, genotype CC may be the most advantageous for growth traits in Nanjiang Huang goats. However, since no information about this SNP of the *IGF-I* gene is available in the literature, further investigations are needed in larger populations of Nanjiang Huang goats, in other goat breeds and in other domestic livestock in order to verify the associated effects of this SNP marker.

CONCLUSIONS

A nucleotide transversion from G to C was identified at intron 4 of the *IGF-I* gene in Nanjiang Huang goats. Two alleles and three genotypes were observed in this group. The results showed that polymorphism of the *IGF-I* gene was associated with BW, W6, W12, G2, L6, H6, H12 and G12 ($p < 0.05$). The goats with genotype CC had significantly higher BW, W6, W12, G2, L6, H6, H12 and

G12 than those with genotype GC, and had significantly higher W12, H6, H12 and G12 than those with genotype GG. The current results indicated that polymorphism of the *IGF-I* gene may be a potential molecular marker for growth traits in Nanjiang Huang goats.

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