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3EFFECT OF G.13700A>G AND G.25783C>T IN PIT-1 GENE ON GROWTH TRAITS OF DUROC, LANDRACE, YORKSHIRE PIG

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ABSTRACT

Pituitary specific transcription factor-1 (*Pit*-1) gene is responsible for pituitary development and growth hormone expression, which is considered a pivotal candidate gene for growth in pig. This study aims to detect novel single nucleotide polymorphisms (SNPs) in porcine *Pit*-1 gene, investigate its effect on growth traits in the Duroc, Landrace and Yorkshire pigs. Two novel polymorphisms were detected, one located in the intron 2 (g. 13700 A>G) and another located in exon 4 (g.25783 C>T) which caused an amino acid change from threonine to methionine (Thr36Met). At g.13700 A>G site, the frequency of A allele was higher than G allele in Duroc, Landrace and Yorkshire. At the g.25783 C>T site, it was remarkable differences in allelic frequencies and genotypic frequencies among the three pig breeds. This study demonstrated the significant genotype effect of *Pit-1* on body weights at 70 d, age when reached 30kg, 50kg, 100kg and average daily gain from 30kg to 100kg. According to our results, the novel *Pit*-1 polymorphisms may be useful in pig selection as molecular markers and required in future studies.

Keywords: *Pit*-1, pig, growth traits, polymorphisms.

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INTRODUCTION

In domestic animals, there are many promising candidate genes for growth distributed in growth hormone (*GH*) axis. *Pit*-1 belongs to POU domain protein family,it is an interdependent gene of *GH* gene pathway (Cogan *et al*. 1998; Negahdary *et al*. 2013). *Pit*-1 controls the development of anterior pituitary and plays regulatory role in gene transcription of pituitary hormone secreting cells, inducing the differentiation of hepatic progenitor cells and delaying human's adrenarche (Lee *et al*. 2005; Taha *et al*. 2005; Tordjman *et al*,2019).

Pit-1 is a specifically expressed transcription factor, which involves in activating the expression of *GH*, prolactin *(PRL)* and thyroid stimulation hormone-β subunit (*TSH-β*) genes (Sudeep *et al*,2016; Tordjman *et al*,2019). It regulates the transcription and expression of these genes and involves in cell differentiation and proliferation (Roche *et al*, 2012), thus plays direct or indirect effects to the growth traits and fatty deposits properties of animals (Forand *et al*, 2016). Li *et al* (1990) reported mutation of *Pit*-1 gene will hinder the secrete of *GH*, *PRL* and *TSH-β* hormones, which causes animal dwarfism. In human and mice, the absence of *Pit*-1 activity results in the lack of multiple pituitary hormones, which leads to dwarfism (Aarskog *et al*.1997; Cohen *et al*. 1999).

Pig's *Pit*-1gene was located on chromosome 13. It was the significant associations between polymorphisms and growth traits of pigs that indicates *Pit*-1 may be a potential candidate gene for growth(Zhao *et al*,2004; Jin *et al*,2018). A polymorphic locus of *BamHI* was found in *Pit*-1 gene in Meishan pigs (Tuggle *et al*.1993) and the polymorphism of *MspI* was found (Yu *et al*.1993). The growth rate and amounts of fat were related to the expression of *Pit-1* in pigs (Andersson *et al*. 1994). In Poland pigs, it was reported that mutations within the *Pit*-1 gene associated with fattening performance (Piórkowska *et al*. 2013). Yu *et al* (1995) found the *MspI* site of *Pit*-1 was related to birth weight and backfat thickness. Yang *et al* (2006) found polymorphism in intron 5 was related significantly to growth traits. Zhang *et al* (2017) reported that the polymorphisms of *RsaI* site of *Pit*-1 gene at exon 5 to intron 5 have a certain effect on pig's growth traits. Moreover, *Pit*-1 polymorphisms within intron 4 to the 3' untranslated region were associated with expected progeny difference (EPD)for production performance in Landrace (Franco *et al*. 2005).

This study detects SNPs of pig's *Pit-1* gene by PCR-SSCP and DNA sequencing, further investigates the relationship between SNPs and growth performance in

three pig breeds. We detected two novel polymorphisms and analyzed with growth traits, which could be useful to pig breeding.

MATERIALS AND METHODS

Animals and Trait Measurements: We used 391 pigs, including 59 Duroc (40 boar and 19 sows), 72 Landrace(46 boar and 26 sows) and 260 Yorkshire(165 boar and 95 sows) pigs, only noninbred individuals for at least 3 generations were included. In 2020, all the pigs were raised in Fuyuefa Livestock and Poultry Breeding limited liability company, Yunnan province, China. Every individual was fed with at least 1.5 square meters in semi-open barn and raised separately by sex. The feeding program includes two feeds: one for growers (weighing from 30 to 70 kg), the energy for growers was at least 13.5 MJ/Kg, the crude protein for growers was between 17%-19%, and the digestible protein for growers was at least 14.0 respectively. Another for finishers (from 70 to 100 kg), energy of feeds for finishers was at least 13.0 MJ/Kg, the crude protein for finishers was between 16%-18%, and the digestible protein for finishers was at least 12.8 respectively. Body weights at born (BW0), body weights at 21d (BW21), body weights at 70 d (BW70) were measured. The age when they reached 30kg (D30), 50kg (D50), 100kg (D100) were recorded by Feed Intake Recording Equipment (Osborne Industries, US). We also measured the ADG from 30kg to 100kg (ADG of 30-100 kg) and the backfat thickness (measure the thickness of Dorsal fat layer by B-mode ultrasound diagnosis instrument, the site was located between the reciprocal third and fourth ribs, 5 cm from dorsal midline)when the body weight reached to 100kg (BFT).

DNA extraction and genotyping: Genomic DNA was extracted from the ear tissues using a standard phenol-chloroform method then quantified using a NanoDrop spectrophotometer (GE Healthcare Life Sciences, Uppsala, Sweden). Genotyping was performed on genomic DNA using PCR-SSCP assays, which was described as follows: 5 μL aliquot of each amplicon was diluted in denaturing solution (98% formamide, 10 mM EDTA, 0.025% bromophenol blue, 0.025% xylene-cyanol) denatured at 95 °C for 5 min, rapidly cooled on ice and resolved in acrylamide: bisacrylamide (29:1) gels at 400 V for 4 h at 4 °C, in 1 × TBE buffer (89 mM Tris base, 89 mM boric acid, 2 mM EDTA, pH 8.0). Then, the gels were silver-stained according to the method of Bassam *et al* (1991). SNPs of the pig *Pit-1* gene (GenBank, accession number NM_214379) were screened from the coding region and partial intron region. The primers used for SNP screening are shown in Table 1. PCR amplifications were carried out in 25 μL reaction volumes containing at the following final concentrations: 50 ng of template DNA, 400 μM of dNTPs (Sangon, China), 0.25 μM of each primer and 1 unit (U) of Taq polymerase (TaKaRa, Japan). The PCR protocol consisted of an initial denaturation at 94 °C for 5 min, followed by 36 cycles of denaturation at 94 °C for 30 s, annealing at 60°C for 30 s, and extension at 72 °C for 30 s, with a final extension at 72 °C for 10 min.

Statistical analysis: Gene frequencies were determined by direct counting. Gene heterozygosity (H) and polymorphism information content (PIC) were calculated according to Nei's and Botstein's methods (Nei and Roychoudhury, 1974; Botstein *et al*., 1980), respectively. The genotype and allele frequencies were tested for Hardy-Weinberg equilibrium using the χ^2 test. The associations analyses were tested with a statistical model using the MIXED model procedures (SAS10; SAS Institute, Inc.). The following model was used:

$$y_{ijk} = \mu + G_i + S_j + e_{ijk}.$$

Where y_{ijk} is observation of traits; μ is population mean; $G_i$is fixed effect of genotypes; S_j is fixed effect of sex; e_{ijk} is random residual error.Least square means and respective standard errors for genotypes were estimated based on the statistical model and significant levels were set at $P \leq 0.05$ and $P \leq 0.01$, respectively.

RESULTS

Detection of single nucleotide polymorphisms: This work amplified nine fragments from genomic DNA by PCR. The PCR products were assayed by the SSCP technique and detect any single base substitution by sequencing the products with unique patterns. Two novel SNPs were identified. One polymorphism was in the intron 2 (g. 13700 A>G). Another one was located in exon 4 (g.25783 C>T) which caused missense mutation, a threonine was changed to methionine (Thr36Met).The g.13700 A>G was one polymorphism in the intron 2 and g.25783 C>T was one substitution located in exon 4. The g.13700 A>G polymorphism showed similar in different breeds, the frequency of A allele was higher than G allele.

Genotype frequencies: In Table 2, it shows the different breeds' allele frequencies and genotype of *Pit*-1 gene SNPs. The polymorphism information content of g.13700 A>G was similar in the experimental individuals and different breeds; it has higher frequency of A allele than Gallele. With respect to this marker, theses three breeds were not at Hardy-Weinberg equilibrium ($P \leq 0.01$). In Duroc, Landrace and Yorkshire breed, H of the mutant loci was 0.4585, 0.4614 and 0.4617, which represented the genetic diversity was relatively abundant. At g.25783 C>T site, frequency of C allele in Duroc, Landrace and Yorkshire was 0.7373, 0.4653 and 0.6654. In Duroc, frequency of the CC genotype was higher than other two genotypes, while the Landrace and Yorkshire breeds were primarily CT genotype.

Relationship between *Pit-1* gene genotypes and growth traits: By association analysis of the growth performance and genotypes in these three breeds, the results are shown in the Table 3. At g.13700 A>G site, in Duroc, individuals with AA genotype had higher D100 than GG genotype ($P \leq 0.05$); individuals with AG genotype had greater BW70 than AA genotype, whereas which had lower D30 ($P \leq 0.01$) in Landrace. The GG genotype had greater ADG of 30-100 kg than other two genotypes ($P \leq 0.05$); individuals with AA genotype had higher D50 but lower ADG of 30-100 kg than GG genotype in Yorkshire ($P \leq 0.01$). At g.25783 C>T site, individuals with TT genotype had lower back fat thickness of 100kg body weight in Duroc ($P \leq 0.05$); individuals with CC genotype had significantly higher D100 but lower ADG of 30-100 kg than genotype TT in Landrace ($P \leq 0.01$). In Yorkshire, genotype TT showed greater in ADG of 30-100 kg compared to genotype CC ($P \leq 0.05$).

Table 1 Segmental amplification primers of *Pit*-1 gene.

sequence of primers (5'→3')	Location	size of products
Forward primer: GTCGCATAAATACCAGCAC Reverse primer: ATTCAAAGCGTCCATCCT	exon 1 12048-12412 bp	365
Forward primer: GTGGATGGATTTGGTC Reverse primer: TTTACTTCCGAGGTTTA	intron1 13587-13780 bp	194
Forward primer: CCAACCTCCTCAATGTCTGTGC Reverse primer: GGTGTCCCAAAACTCAATCTCA	exon2 15698-15868 bp	173
Forward primer: CAGATAGAAATGGGGGATAA Reverse primer: GGGATTGAACAGTAACAGAGTA	exon3 23488-23838 bp	351
Forward primer: TTTCACAGGATACACCCAA Reverse primer: GCTTCCTCCAGCCATT	exon4 25742-25907 bp	166
Forward primer: GACTATTTGCCGATTTGA Reverse primer: ACTTGCCTTGCTATGTGA	intron4 25888-26134 bp	247
Forward primer: GCAAAAACAACTGAAAAATGTATGG Reverse primer: AGGCTGTGGTGTAGGCTGGT	exon5 26482-26800 bp	319
Forward primer: AACGAACAACAATCAGG Reverse primer: TTGCTCAGTGGGTTAAGGGT	intron5 27269-27486	218
Forward primer: CCATCTCACACCTCCCAGTA Reverse primer: CTCTGCCTTCGGTTGC	exon6 27452-27605	154

Table 2 The genotypic and allelic frequencies of *Pit*-1 gene SNPs in different pig breeds.

SNP site	breed	genotype	genotypic frequency	allele	allelic frequency	χ^2	*H*	*PIC*
		AA	0.542(32)	A	0.644			
	D	AG	0.203(12)			18.3**	0.459	0.353
		GG	0.254(15)	G	0.356			
		AA	0.514(37)	A	0.639			
A13700G	L	AG	0.250(18)			15.1**	0.461	0.355
		GG	0.236(17)	G	0.361			
		AA	0.523(136)	A	0.639			
	Y	AG	0.231(60)			65.0**	0.462	0.355
		GG	0.246(64)	G	0.362			
		CC	0.525(31)	C	0.737			
	D	CT	0.424(25)			0.519	0.387	0.312
		TT	0.0508(3)	T	0.263			
		CC	0.278(20)	C	0.465			
C25783T	L	CT	0.375(27)			4.37*	0.498	0.374
		TT	0.347(25)	T	0.535			
		CC	0.404(105)	C	0.665			
	Y	CT	0.523(136)			7.93**	0.445	0.346
		TT	0.0731(19)	T	0.335			

Note：D: Duroc , L: Landrace, Y: Yorkshire; *: $P \leq 0.05$,**: $P \leq 0.01$. $3.84 < \chi^2 < 6.63$ represents $P \leq 0.05$, $\chi^2 > 6.63$：$P \leq 0.01$.

Table 3 Least squares means ± SE for growth traits among genotypes of 2 SNPs in *Pit-1* gene.

Site	breed	genotype	N	BW0	BW21	BW70	D30	D50	D100	ADG of 30-100 kg	BFT
		AA	32	1.84±0.06	7.59±0.11	28.15±0.40	72.74±0.67	101.47±0.68	169.11±0.89^{a}	730±8	9.38±0.19
	D	AG	12	1.82±0.09	7.52±0.17	27.38±0.62	73.94±1.04	101.87±1.05	168.02±1.38^{ab}	748±12	9.53±0.30
		GG	15	1.88±0.09	7.36±0.17	27.83±0.55	73.00±0.93	101.59±0.94	165.69±1.23^{b}	757±11	9.20±0.27
		AA	37	1.73±0.03	7.20±0.15	26.62±0.42^{bB}	74.94±0.70^{aA}	103.28±0.72	168.71±0.82	715±12^{b}	9.36±0.18
A13700G	L	AG	18	1.69±0.05	7.11±0.23	28.67±0.57^{aA}	71.35±0.96^{bB}	102.22±0.99	168.80±1.12	730±10^{ab}	9.19±0.25
		GG	17	1.77±0.05	7.09±0.24	28.47±0.67^{aAB}	71.88±1.13^{bAB}	102.58±1.17	169.85±1.31	759±8^{a}	9.51±0.29
		AA	136	1.72±0.02	7.31±0.09	26.77±0.22	74.12±0.40	103.32±0.41^{A}	169.42±0.45	720±6^{bB}	9.43±0.09
	Y	AG	60	1.74±0.03	7.10±0.11	27.44±0.33	73.22±0.62	100.76±0.62^{B}	170.70±0.68	723±7^{bAB}	9.66±0.14
		GG	64	1.72±0.05	7.44±0.20	27.13±0.32	73.22±0.60	100.70±0.60^{B}	170.96±0.66	741±4^{aA}	9.67±0.13
		CC	31	1.77±0.08	7.60±0.16	27.83±0.41	72.97±0.69	101.71±0.70	169.02±0.93	733±8	9.69±0.19^{a}
	D	CT	25	1.89±0.06	7.60±0.11	27.81±0.43	73.39±0.73	101.44±0.74	166.96±0.98	749±9	9.15±0.20^{a}
		TT	3	1.83±0.14	7.18±0.28	28.92±1.27	71.74±2.15	101.63±2.16	168.97±2.88	721±25	8.45±0.59^{b}
		CC	20	1.73±0.07	7.14±0.31	28.49±0.57	71.65±0.97	100.85±0.90	170.68±1.04^{aA}	709±10^{B}	9.45±0.24
C25783T	L	CT	27	1.64±0.06	7.23±0.28	26.88±0.47	73.82±0.81	102.62±0.75	167.90±0.87^{bAB}	756±9^{A}	9.36±0.20
		TT	25	1.77±0.04	7.14±0.17	28.16±0.57	72.98±0.98	100.94±0.90	166.62±1.05^{bB}	749±10^{A}	9.18±0.24
		CC	105	1.75±0.03	7.30±0.13	27.20±0.25	73.33±0.46	102.93±0.48	170.80±0.50	729±5^{b}	9.50±0.10
	Y	CT	136	1.74±0.02	7.23±0.09	26.84±0.22	73.89±0.41	102.09±0.43	169.19±0.46	741±4^{a}	9.58±0.09
		TT	19	1.68±0.03	7.28±0.14	27.02±0.59	72.60±1.09	102.52±1.13	168.92±1.20	742±12^{a}	9.50±0.25

Note: Among genotypes within each SNP for each trait, ^{A,B} means without a common superscript differ ($P \leq 0.01$).$^{a-b}$ means without a common superscript differ ($P \leq 0.05$). n indicates the number of individuals. BW21, BW70 represents body weight at 49 and 70 days. D30, D50, D100 represents days to 30 ,50, 100 kg body weight, BFT represents the backfat thickness of 100kg body weight.

DISCUSSION

In animal production, the underlying genetic nature of traits with economic interest is complex and manifests as continuous variation. Growth traits are influenced by both genetic factors and environment. Due to the current availability of neutral polymorphisms, identifying the chromosome regions which effect growth performance could be achieved (Molaee *et al*. 2009; Negahdary *et al*. 2013). For *Pit*-1 gene polymorphisms, several studies have been done (Xu *et al*,2015; Jin *et al*,2018; Zhang *et al*,2020; Sakar,2022). It was supposed by SSCP analysis of genes that those genes could have associations with growth traits, which helps establish the allelic variants as markers to aid in selection.

This study showed *Pit*-1's significant genotype effect on growth performance of pigs. However, the same genotype in different pig breed which was associated with different phenotype. Thus, the associations identified in this report may be caused by linkage disequilibrium (LD) to a linked QTL instead of related to function of *Pit*-1 gene. In this connection, Yu *et al*. used haplotype analysis to show that LD is significant in the region surrounding *Pit*-1 for backfat in Meishan × commercial crosses (Yu *et al*. 1995; Yu *et al*. 1999). This implied that the linkage disequilibrium of *Pit*-1 with another locus may explain the pronounced discrepancies about its possible genotype effects among labs. The region near *Pit*-1 on pig chromosome 13 was associated with backfat thickness (Bidanel *et al*. 2001) according to QTL mapping research. Franco confirmed that *Pit*-1 polymorphisms were associated with fat thickness and average daily gain (Franco, *et al*. 2005).Stančeková *et al* reported that DD genotype of *Msp*I site in *Pit*-1 gene was associated with significantly better backfat thickness in European Large White pigs and a crossbred population of Large White × Landrace. In Landrace breed, it was found that CC genotype significantly reduced backfat thickness and increased Lean meat percentage, eye muscle area and hind legs proportion (Liu *et al*. 2009). In this study, we did not detect *Pit*-1 *MspI* in the three populations. But, at the g.25783 C>T site, in Duroc breed, individuals with TT genotype had lower BFT ($P \leq 0.05$).

Overall, in this study, two novel SNPs of *Pit-1* gene were identified. Genotypic and allelic frequencies of g.13700 A>G and g.25783 C>T significantly differed among the three pig breeds. This study indicates that polymorphism may be contributed to variation in traits analyzing, and enable these polymorphisms to contribute to breeding programs and molecular marker-assisted selection.

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