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A combined genotype of three SNPs in the bovine *PPARD* gene is related to growth performance in Chinese cattle

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Abstract. *PPARD* is involved in multiple biological processes, especially for those associated with energy metabolism. *PPARD* regulates lipid metabolism through up-regulate expression of genes associating with adipogenesis. This makes *PPARD* a significant candidate gene for production traits of livestock animals. Association studies between *PPARD* polymorphisms and production traits have been reported in pigs but are limited for other animals, including cattle. Here, we investigated the expression profile and polymorphism of bovine *PPARD* as well as their association with growth traits in Chinese cattle. Our results showed that the highest expression of *PPARD* was detected in kidney, following by adipose, which is consistent with its involvement in energy metabolism. Three SNPs of *PPARD* were detected and used to undergo selection pressure according the result of Hardy–Weinberg equilibrium analysis ($P < 0.05$). Moreover, all of these SNPs showed moderate diversity ($0.25 < \mathrm{PIC} < 0.5$), indicating their relatively high selection potential. Association analysis suggested that individuals with the GAAGTT combined genotype of three SNPs detected showed optimal values in all of the growth traits analyzed. These results revealed that the GAAGTT combined genotype of three SNPs detected in the bovine *PPARD* gene was a significant potential genetic marker for marker-assisted selection in Chinese cattle. However, this should be further verified in larger populations before being applied to breeding.

1 Introduction

Peroxisome-proliferator-activated receptors (PPARs) are a group of transcription factors belonging to the nuclear hormone receptor superfamily (Evans et al., 2004). Many studies have revealed PPARs take part in numerous biological processes, including lipid metabolism, the insulin signaling pathway, glucose metabolism, and adipocyte differentiation (Youssef and Badr, 2013). To date, three subtypes of PPARs have been discovered: *PPARA*, *PPARD*, and *PPARG*. Among these, *PPARD* is widely expressed in various tissues, including kidney, liver, heart, intestine, and adipose (Abbott, 2009). *PPARD* regulates lipid metabolism through up-regulate expression of genes involved in the adipogenesis process (Vedhachalam et al., 2007). Recently, studies have suggested that *PPARD* is essential for adipogenesis as well (Garbacz et al., 2015; Barroso et al., 2015; Palomer et al., 2016).

Genetic variation in *PPARD* is proved to be associated with human diseases. The *PPARD* rs2016520 polymorphism was reported to affect repaglinide response in Han Chinese patients with type 2 diabetes mellitus (Song et al., 2015). Furthermore, this mutation was shown to be associated with brain diseases (Huang et al., 2015) and colorectal cancer (Rosalesreynoso et al., 2017). For its vital role in various biological processes, *PPARD* is a potential gene affecting production traits of livestock animals. Polymorphisms of *PPARD* were shown to affect ear size (Ren et al., 2011) and litter size (Spötter et al., 2010) in pigs. Recently, functional SNPs in the 5′ regulatory region of the porcine *PPARD* gene have been reported to be significantly associated with fat deposition traits (Zhang et al., 2015). However, association studies between *PPARD* and production traits in other animals are limited, including cattle.

Marker-assisted selection (MAS) has been widely used as a breeding strategy in livestock (Margawati, 2012). To detect functional SNPs of *PPARD* for MAS in cattle, we (i) analyzed the expression profile of *PPARD* in different tissues, (ii) detected SNPs in the bovine *PPARD* gene by direct sequencing using 514 Chinese cattle, and (iii) assessed the relationship between detected SNPs and growth traits in partial cattle.

2 Material and methods

2.1 Samples

Samples used in this study were shown in a previous study (Huang et al., 2017). Briefly, seven tissues were collected at the slaughter house for reverse transcription polymerase chain reaction (RT-PCR), including heart, liver, spleen, lung, kidney, muscle, and adipose of three Jiaxian cattle (bullock, 30 months). A total of 514 individuals from six Chinese cattle breeds – including 141 Jiaxian cattle, 139 Nanyang cattle, 114 Luxi cattle, 30 Qinchuan cattle, 30 Bohai, cattle and 60 Gaoyuan yak – were used for SNP genotyping. Birth weight and six growth traits (body weight, body height, body length, heart girth, hip width, and average daily gain) of Jiaxian and Nanyang cattle at 6, 12, 18, and 24 months as well as nine traits (body height, body length, heart girth, abdominal circumference, hip width, sciatic width, height at hip cross, body weight, and beef performance index) at around 28–30 months of age in 300 Henan cattle (100 Jiaxian, 100 Nanyang, and 100 Luxi) were recorded for association analysis.

2.2 Expression analysis of *PPARD*

In order to understand the potential biological effect of *PPARD* on cattle, expression levels of *PPARD* in seven tissues were investigated by RT-PCR. Details of the method are shown in a previous study (Huang et al., 2017). Total RNA was reversely transcribed into cDNA using a PrimeScript-sRT reagent kit with gDNA Eraser (TaKaRa, Japan). RT-PCR was performed using SYBR Green I with two-step reactions. Primers of *PPARD* (NM_001083636.1) and reference genes (*TUBA1A,* NM_001166505.1; β-actin, NM_173979.3) for RT-PCR are shown in Table S1 (Supplement). The relative expression level of each tissue was presented as mean ±SD.

2.3 SNP detection and genotyping

In order to investigate polymorphism of *PPARD* (AC_000180.1) in Chinese cattle, nine pairs of primers covering CDS and partial upstream regions were synthesized (Table S1). The methods for SNP detection and genotyping were as in a previous study (Huang et al., 2017). Pooled DNA samples were used as a PCR template for SNP detection. For SNPs detected (Table 1), three pairs of specific primers were designed (Table 2). The traditional PCR-RFLP method was used for SNP genotyping in 514 Chinese cattle from six breeds. It should be noted that PCR production of PPARD-MluI primers contained two recognition sites of MluI, one of which was native and the other was introduced from primers for genotyping.

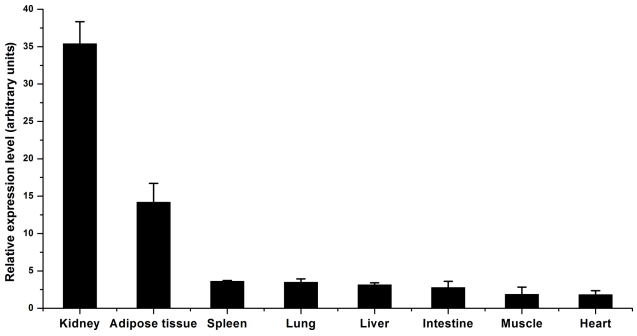

Figure 1. Tissue distribution of bovine *PPARD* mRNA assessed by RT-PCR. Values shown in this figure are averages of three independent experiments. Error bars represent SD ($n = 3$) of relative mRNA levels. Expression data were normalized using geometric mean of mRNA levels for two control genes (*TUBA1A* and β-actin).

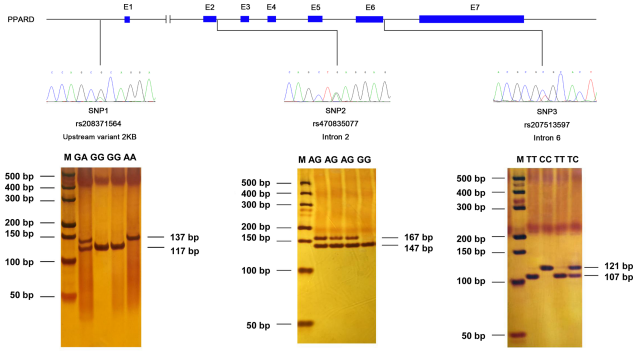

Figure 2. Schematic characteristic of SNPs identified in bovine *PPARD* and genotyping. From top to bottom: structure of bovine *PPARD*, mutant peaks of sequencing, details of SNPs identified, and electrophoretogram of genotyping.

2.4 Statistical analysis

The genetic characteristics of each mutation were investigated after genotyping, including allele frequencies, Hardy–Weinberg equilibrium (HWE), heterozygosity (H_e), effective allele numbers (N_e), and polymorphism information content (PIC). To evaluate the potential relationship between the *PPARD* gene and development of cattle, an association study was performed based on the genotyping results and growth traits in Nanyang, Jiaxian, and Luxi cattle. Significant analysis was performed by SPSS 19.0 using general linear model. Results were presented as means ±SE. Other details can be found in a previous study (Huang et al., 2017).

Table 1. Details of SNPs detected in the bovine *PPARD* gene.

Label	Position	Alleles	rs number	Functional consequence
SNP1	AC_000180.1: 9268142	G > A	rs208371564	upstream variant 2KB
SNP2	AC_000180.1: 9341130	A > G	rs470835077	intron 2
SNP3	AC_000180.1: 9352706	T > C	rs207513597	intron 6

Table 2. Details of primers and restriction enzymes used for genotyping.

Name	Primer sequence (5′-3′)	T_m (°)	Size (bp)	Used for	Restriction enzyme	Main fragments
PPARD -Hha I	F:GCAGGATATAGTTCCCAGC R:GACTTGTCATCCCAACCTT	55	137	SNP1	Hha I	GG: 117 bp GA: 137 bp, 117 bp AA: 137 bp
PPARD -Pvu II	F:TCCTTCCAGCAGCTACACAG CT R:GGGAGACAACTCGCCCAAG A	57.5	195	SNP2	Pvu II	GG: 147 bp AG: 167 bp, 147 bp
PPARD -Mlu I	F:ATGGCAGTGGGACACGCG R:CCACCAGAAATAACCCCCAT C	63	121	SNP3	Mlu I	TT: 107 bp TC: 121 bp, 107 bp CC: 121 bp

Note: letters underlined in the primer sequence are the introduced mutant for genotyping.

3 Results and discussion

3.1 Expression profile of *PPARD*

The expression profile of *PPARD* has been widely investigated in rodent and human development, but it is limited in cattle. In order to understand the potential biological effect of *PPARD* on cattle, expression levels of *PPARD* were investigated (Fig. 1). Consistent with previous studies, *PPARD* was widely expressed in main tissues, suggesting that it was involved in multiple biological processes. The highest level of expression was detected in kidney, followed by adipose tissue (Fig. 1), indicating its significant biological role in kidney and adipose tissues. Expression levels of the *PPARD* gene in the other six tissues were nearly the same, with relatively low values. In fact, the expression pattern of *PPARD* was found to be variable in different studies. *PPARD* was expressed in kidney with a high level in adult rats (Braissant and Wahli, 1996), adult mice (Girroir et al., 2008), and adult human (Auboeuf et al., 1997). PPARs were identified as the genetic sensor responsive to fatty acid ligands (Feige et al., 2006) and involved in lipid metabolism and the insulin signaling pathway (Youssef and Badr, 2013). In addition, chronic kidney disease was attributed to metabolic disorders mainly through the mechanisms of insulin resistance and resultant hyperinsulinemia (Perlstein et al., 2007). In fat tissue, only a moderate level was detected in adult rats and humans (Braissant and Wahli, 1996; Auboeuf et al., 1997). These results were consistent with our study. However, a moderate to high level of expression in liver, heart, and lung was detected in adult rodents and humans (Girroir et al., 2008; Tugwood et al., 1996; Mukherjee et al., 1997), which was nearly contradictory with our result. Regardless, all of these results underline multiple functions of *PPARD* in the development of mammals. Thus, *PPARD* should be necessary for cattle development.

3.2 SNP detection and genetic characteristics of *PPARD* in Chinese cattle

In total, three SNPs were detected (Table 1 and Fig. 2), including AC_000180.1:g.9268142 G > A in the upstream

Table 3. Association analysis between combined genotypes of three SNPs in *PPARD* and growth traits of 300 adult cattle.

Growth traits	Combined genotypes								
	GAAGCC (10)	GAAGTC (66)	GAAGTT (35)	GAGGTC (45)	GAGGTT (21)	GGAGTC (29)	GGAGTT (14)	GGGGTC (41)	GGGGTT (20)
BH (cm)	129.450 ± 3.028	129.106 ± 1.179	130.843 ± 1.618	130.033 ± 1.427	129.286 ± 2.089	129.448 ± 1.778	127.286 ± 2.559	131.598 ± 1.495	127.450 ± 2.141
BL (cm)	145.900 ± 4.034	144.068 ± 1.570	147.743 ± 2.156	143.500 ± 1.901	143.619 ± 2.783	143.017 ± 2.369	146.643 ± 3.409	145.415 ± 1.992	141.750 ± 2.852
HG (cm)	171.400 ± 5.195	174.538 ± 2.022	176.414 ± 2.777	174.156 ± 2.449	168.214 ± 3.585	169.414 ± 3.051	171.357 ± 4.391	175.634 ± 2.566	168.750 ± 3.673
AC (cm)	200.100 ± 6.774	203.008 ± 2.637^{ab}	205.514 ± 3.621^{a}	204.156 ± 3.193^{a}	192.476 ± 4.674^{b}	199.069 ± 3.978	200.143 ± 5.725	201.415 ± 3.345	190.700 ± 4.790^{bc}
HW (cm)	45.200 ± 1.897^{a}	45.023 ± 0.738^{a}	45.471 ± 1.014^{a}	45.344 ± 0.894^{A}	43.310 ± 1.309	44.190 ± 1.114	45.286 ± 1.603^{a}	43.341 ± 0.937	41.100 ± 1.341^{Bb}
SW (cm)	28.500 ± 1.456^{A}	28.659 ± 0.567^{A}	28.586 ± 0.778^{A}	27.489 ± 0.687^{A}	27.548 ± 1.005^{A}	26.914 ± 0.855^{A}	28.107 ± 1.231^{A}	25.549 ± 0.719^{a}	22.600 ± 1.030^{Bb}
HHC (cm)	129.300 ± 2.691	129.394 ± 1.048	131.357 ± 1.438	129.122 ± 1.269	129.238 ± 1.857	131.621 ± 1.580	128.214 ± 2.274	132.232 ± 1.329	128.575 ± 1.903
BW (kg)	391.453 ± 32.883	388.720 ± 12.800	413.462 ± 17.577^{a}	399.380 ± 15.501	385.273 ± 2.691	391.784 ± 19.310	378.964 ± 27.791	391.686 ± 16.240	350.251 ± 3.252^{b}
BPI (kg cm^{-1})	3.017 ± 0.194	3.001 ± 0.076	3.113 ± 0.104^{a}	3.045 ± 0.092	2.906 ± 0.134	2.987 ± 0.114	2.962 ± 0.164	2.956 ± 0.096	2.738 ± 0.137^{b}

BH: body height; BL: body length; HG: heart girth; AC: abdominal circumference; HW: hip width; SW: sciatic width; HHC: height at hip cross; BW: body weight; BPI: beef performance index.
Lowercase letters mean difference of the value at $P<0.05$; uppercase letters mean difference of the value at $P<0.01$.

region (SNP1, rs208371564), AC_000180.1:g.9341130 A>G in intron 2 (SNP2, rs470835077), and AC_000180.1:g.9352706 T>C in intron 6 (SNP3, rs207513597). A total of 3801 SNPs of the bovine *PPARD* gene can be searched in the SNP database of NCBI (https://www.ncbi.nlm.nih.gov/snp/), including 710 detected by cluster and 3091 with no information. No more SNPs could be found from other studies. Thus, the three SNPs detected in this study were not further analyzed although they had been detected by cluster previously.

Then, genetic characteristics of SNPs were investigated based on the genotyping result (Table S2). We noted that the AA genotype of SNP2 was absent in all of the populations in this study. At the same time, the A allele was not rare in Chinese cattle. Therefore, we speculated that individuals with the AA genotype of SNP2 died during the embryonic stage or were culled because of disease at an early age. Amazingly, approximately half of the breeds were not in agreement with the HWE ($P<0.05$) at each of these SNP loci, suggesting that they might undergo selection pressure. All of the three SNP loci showed moderate diversity ($0.25<\text{PIC}<0.5$), indicating their relatively high selection potential. Further selection could be implied if a positive effect were found among these SNPs in cattle breeds investigated.

3.3 Association study between *PPARD* and growth traits

Potential genomic mutations of the *PPARD* gene might be related to growth traits of cattle. First, relationship between *PPARD* and growth traits were investigated in 173 Henan cattle based on a single SNP locus (Table S3). Several significant differences were identified without regularity. Generally, the phenotypic value should change along with the variation in genotype (in the order of wild type, heterozygous type, and homozygous mutant type) with a specific trend. Moreover, this trend should be the same among different breeds and ages. However, significant differences detected in Table S3 did not conform to such trends and showed disorder. This might be due to the low sample size, or else multiple loci affect the same traits with different weight. Therefore, it was hard to estimate the real association between these SNPs and growth traits in cattle.

We speculated that coordination among multiple SNPs loci might contribute to development or be linked with

growth traits of cattle. Based on such a hypothesis, association analysis between combined genotypes of these three SNPs and growth traits of 300 adult cattle was performed. Combined genotypes with less than 10 individuals were removed. In total, nine combined genotypes were used for analysis (Table 3). Interestingly, all traits showed the highest values in the GAAGTT combined genotype. Among these, abdominal circumference, hip width, sciatic width, body weight, and beef performance index showed significant differences. Obviously, individuals with the GAAGTT combined genotype of these three SNPs showed optimal growth performance. In fact, association analysis based on combined genotype has been widely used in studies on the relationship between genetic variation and diseases in humans (Kamitani et al., 1995; Boulet et al., 2008; Stelma et al., 2016) and traits in livestock animals (Garaulet et al., 2012). However, results from this analytical method need further verification from multiple points. The bovine *PPARD* gene is identified in chromosome 23 (9.27–9.36 Mb). By searching the quantitative trait locus (QTL) database of cattle (http://www.animalgenome.org/cgi-bin/QTLdb/BT/browse) for those QTLs associated with growth trait, four QTLs were obtained, including a QTL (5.9–16.3 Mb) for body weight of adult cattle (McClure et al., 2010), a QTL (0.6–17.5 Mb) for body weight before slaughter (Elo et al., 1999), a QTL (7.2–21.1 Mb) for body weight at weaning (McClure et al., 2010), and a QTL (7.2–21.1 Mb) for body weight at 12 months (McClure et al., 2010). These QTLs further suggested that *PPARD* was a potential significant candidate gene for production traits of cattle. Three SNPs identified in this study were in the non-coding region. In recent years, transcripts (non-coding RNAs) from non-coding region have been shown to regulate the transcription of the origin genes and then affect the biological function of the origin genes. However, the non-coding region might provide the binding site for some enzymes relating to transcription. Thus, mutations in the non-coding region could play a role in the regulation mechanism. However, SNPs may only be markers associated with production traits and do not affect any biological process.

4 Conclusions

The bovine *PPARD* gene is expressed widely in the main tissues of adult cattle. Three SNPs of *PPARD* were identified in Chinese cattle. The GAAGTT combined genotype of these three SNPs showed optimal growth performance, which could be a potential marker for MAS of cattle. However, further identification should be performed in larger populations before being applied to breeding of cattle.

Data availability. The original data are available upon request from the corresponding author.

The Supplement related to this article is available online at https://doi.org/10.5194/aab-60-357-2017-supplement.

Author contributions. YM and FL designed experiments and collected samples. QZ, SW, QZ, LJ and RH carried out the experiment; JH analyzed the data and wrote the manuscript.

Competing interests. The authors declare that they have no conflict of interest.

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