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ASSOCIATION OF SNPS IN *AKIRIN2*, *TTN*, *EDG1* AND *MYBPC1* GENES WITH GROWTH AND CARCASS TRAITS IN QINCHUAN CATTLE*

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Abstract

Growth and carcass traits are the main breeding objectives in beef cattle. The aim of this study was to confirm genetic effects of the *c.*188G>A* SNP of *AKIRIN2*, the *g.231054C>T* SNP of *TTN*, the *g.1471620G>T* SNP of *EDG1* and the *g.70014208A>G* SNP of *MYBPC1* on growth and carcass traits in Chinese Qinchuan (QC) cattle, as well as to compare the frequencies of the well-characterized alleles of these SNPs among six Chinese cattle populations, three Japanese cattle populations, two European cattle populations and one Korean cattle population. In this study, a total of 665 cattle samples were genotyped using MassARRAY and PCR-RFLP. Association analysis explored effects of four SNPs on growth and carcass traits including body length, wither height, hip height, hip width, rump length, chest depth, chest circumference, back fat thickness, ultrasound longissimus muscle area and ultrasound longissimus muscle depth in QC (P<0.05 to P<0.001). The well-characterized *A* (*c.*188G>A*), *T* (*g.231054C>T*) and *T* (*g.1471620G>T*) alleles in Japanese Black cattle were significantly higher than Chinese cattle breeds; on the contrary, the *G* allele

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(*g.70014208A>G*) was markedly higher in Chinese cattle breeds than other cattle breeds. These results suggest that the four SNPs might be useful as a molecular marker for growth-related traits in Chinese QC cattle.

Key words: association, candidate genes, economic traits, SNPs, Qinchuan cattle

Growth and carcass traits are complex and controlled by multiple genes (Andersson, 2001; Andersson and Georges, 2004), which have an important effect on the economics of beef production. Thus, a better knowledge of the molecular architecture of growth and carcass traits is important as it may generate new opportunities for more effective marker-assisted selection, leading to economic benefits to the beef production industry (Raza et al., 2020 a).

To date, numerous candidate genes and molecular markers associated with economic traits of beef cattle have been identified, and some of them have already been used in cattle breeding (Raza et al., 2019; Yamada, 2014; Raza et al., 2020 b). Among them, the *akirin 2 (AKIRIN2)* gene is located within genomic regions of quantitative trait loci (QTLs) for marbling score and longissimus muscle area in Japanese Black (JB) cattle (Takasuga et al., 2007), as well as marbling score in Angus cattle (McClure et al., 2010); the *titin* (*TTN*) gene was found in the genomic regions within QTLs for marbling score, longissimus muscle area and subcutaneous fat thickness in JB (Takasuga et al., 2007), as well as subcutaneous fat thickness in a Brahman × Hereford sire developed half-sib family (Casas et al., 2003); the *endothelial differentiation sphingolipid G-protein-coupled receptor 1 (EDG1)* gene is located within genomic regions of QTLs for marbling score and body weight in JB (Takasuga et al., 2007), subcutaneous fat thickness in Angus (Mateescu et al., 2017), as well as marbling score in a Belgian Blue × MARC III developed half-sib family and a Piedmontese × Angus sire developed half-sib family (Casas et al., 2001), and the *myosin binding protein C, slow type* (*MYBPC1*) is included in the genomics regions of QTLs for rib thickness and subcutaneous fat thickness in JB (Takasuga et al., 2007), marbling score in Angus (McClure et al., 2010), hip height, rump length, rump width and chest depth in a cattle population including 1554 AI bulls distributed in 14 half-sib families (nine in Holstein, three in Normande and two in Montbéliarde breeds) (Boichard et al., 2003), as well as intramuscular fat in a Brangus heifers population (Peters et al., 2012). Thus, these genes could be considered as important candidate genes for carcass and growth traits in beef cattle. Furthermore, the *c.*188G>A* single nucleotide polymorphism (SNP) in the 3' untranslated region (UTR) of *AKIRIN2*, the *g.231054C>T* SNP in the promoter region of *TTN*, the *g.1471620G>T* SNP in the promoter region of *EDG1* and the *g.70014208A>G* SNP in the promoter region of *MYBPC1*, showed associations of these SNPs with growth or carcass traits in JB (Sasaki et al., 2009; Yamada et al., 2009 a, b, 2011; Tong et al., 2014 a, 2015) and Korean native (KN) (Kim et al., 2013) cattle. However, the relationships of these SNPs with growth and carcass traits in Chinese cattle breed have not been investigated.

Chinese indigenous cattle breeds can be divided into three groups based on their geographic distribution, morphological characteristics and sex chromosome poly-

morphisms: the northern type in North China (NC), the central type in the middle (CC) and lower areas of the Yellow River and the southern type in South China (SC) (CNCAGR, 2011). The Qinchuan (QC) cattle, which is a typical breed of CC, are well-known to be good beef cattle in China, because of distinctive qualities including good adaptability and fine beef flavor among others. However, QC cattle exhibit a number of limitations compared to imported commercial beef cattle breeds, such as slow growth rate and underdeveloped hind hips. Accordingly, it is necessary to select important functional genes and molecular marker to increase the economic traits of Chinese native cattle (Tong et al., 2017; Wang et al., 2020).

Therefore, the objectives of this study reported herein were to: (1) perform association analyses of these SNPs in the *AKIRIN2*, *TTN*, *EDG1* and *MYBPC1* genes with growth and carcass traits in QC, (2) investigate the genetic diversity of these SNPs in three Chinese typical cattle groups (including QC, Mongolia cattle (MG), Luxi (LX), Wuling (WL) and Longlin (LL) cattle breeds), and (3) compare the frequencies of the well-characterized alleles of these SNPs in Chinese cattle breeds to those of JB, Japanese Brown (JBR), Japanese Short Horn (JSH), Holstein (HOL), Brown Swiss (BS) (Watanabe et al., 2010, 2011; Tong et al., 2014 b) and KN breeds (Kim et al., 2013).

Material and methods

Ethics standards and animals

The animals handling and experiments were conducted according to the guidelines laid down by Ministry of Science and Technology, 2004 China. The protocol was approved by the Institutional Animal Care and Ethics Committee of Inner Mongolia University, notified vide notification No.IMU-2018-01, dated 01-03-2018. The 41 MG population from Inner Mongolia Autonomous Region of China (MGC) and 24 LX cattle were sampled from Chifeng Shengquan Ecological Animal Husbandry Co., Ltd. Ten milliliters of blood was collected from each cattle for DNA extraction.

Samples and phenotypic data

Genomic DNA of 41 MGC and 24 LX were extracted from blood samples with a TIANamp Blood DNA kit (TIANGEN Biotech, Beijing, China). The quality and quantity of the extracted DNA were evaluated using a Nanodrop® spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA) and by agarose gel electrophoresis. The DNA samples and phenotypes of 350 QC adult females (24–30 months, non-pregnant) were provided from Northwest A & F University, Yangling, China (Wu et al., 2018; Raza et al., 2020 b, c, d). Animals were chosen at random from the National Beef Cattle Improvement Center herd (Yangling, China). All cows were fed the same total mixed ration with a roughage to concentrate ratio of 3:2. The herd was managed under the same conditions (temperature, humidity etc.). The feeding was offered based on NRC standards (Nutrient Requirement of Beef Cattle, 2016). The growth traits including body length, withers height, hip height, hip width, rump

length, chest depth and chest circumference were estimated as per standard procedure (Wu et al., 2018; Raza et al., 2020 b, c, d). The carcass traits including back fat thickness, ultrasound loin muscle area and ultrasound loin muscle depth were estimated using ultrasound technology (Sono-grader ultrasound machine, Renco, USA). The phenotypic traits were measured through ultrasonography, because ultrasound measurement predicts carcass quality traits in live animals in a nondestructive manner. The ultrasonic probe was placed in the area between the 12th and 13th ribs (Wu et al., 2018; Raza et al., 2020 b, c, d). The DNA samples of 50 MG population from Mongolia (MGM), 50 WL and 50 LL cattle were provided from the Inner Mongolia Key Laboratory of Biomanufacture, Inner Mongolia Agriculture University. The information of cattle breeds in this study is shown in Table 1.

Table 1. Information of six cattle populations selected for genotyping

Breed	Abbreviation	Number	Type
Mongolia cattle population (Inner Mongolia Autonomous Region of China)	MGC	41	North China (NC)
Mongolia cattle population (Mongolia)	MGG	50	North China (NC)
Qinchuan cattle	QC	350	Central China (CC)
Luxi cattle	UM	24	Central China (CC)
Wuling cattle	WL	50	South China (SC)
Longlin cattle	LL	50	South China (SC)

Genotyping using iPLEX MassARRAY

For 350 QC cattle population, the *c.*188G>A* SNP of *AKIRIN2*, the *g.231054C>T* SNP of *TTN*, the *g.1471620G>T* SNP of *EDG1* and the *g.70014208A>G* SNP of *MYBPC1* were genotyped with the MassARRAY® SNP genotyping system (Agena Bioscience, San Diego, CA, USA). PCR and extension primers were designed from sequences containing each target mutation and ~ 100 upstream and downstream bases with Assay Design Suite (http://agenabio.com/assay-design-suite-20-software) using the default settings. The genotype of each allele was analyzed using the Sequenom MassARRAY iPLEX platform (Gabriel et al., 2009). The resulting data was analyzed using the MassARRAY Typer 4.0 Analyzer software (Agena Bioscience, San Diego, CA, USA).

Genotyping using PCR-RFLP

For 41 MGC, 50 MGM, 50 WL, 50 LL and 24 LX cattle populations, the *c.*188G>A* SNP of *AKIRIN2*, the *g.231054C>T* SNP of *TTN*, the *g.1471620G>T* SNP of *EDG1* and the *g.70014208A>G* SNP of *MYBPC1* were genotyped using PCR-restriction fragment length polymorphism (RFLP) method as described previously (Sasaki et al., 2009; Yamada et al., 2009 a, b; Tong et al., 2014 a). The PCR primers and restriction enzymes used for PCR-RFLP are shown in Table 2.

Table 2. PCR primers and restriction enzymes used for PCR-RFLP method

Gene	SNP	Primers (5'-3')	Restriction enzyme	Reference
AKIRIN2	*c.*188G>A*	TCTTAGGCAGCAACCGGATT	*Fok*I	Sasaki et al., 2009
		GAAGGGCATGTTCTTAGAATACCAG		
TTN	*g.231054C>T*	TCATCTCCTAACTACTTCCCA	*Hpy*CH4III	Yamada et al., 2009 a
		ACAAAATCTGAACCTGGCTT		
EDG1	*g.1471620G>T*	GTGTTAATATGTATGAAGCTTGATAGTCAGGAAATAAAT	*Mlu*CI	Yamada et al., 2009 b
		CCACTGTATCGCTGAGCTAGGT		
MYBPC1	*g.70014208A>G*	GATCCCATGGACTACAGCCTACC	*Bgl*II	Tong et al., 2014 a
		ACGGTAAAGCGACTGCCTACA		

Genetic diversity analysis

Genotypic and allelic frequencies for all four SNPs of QC, MGC, MGG, WL, LL and LX cattle populations were calculated directly. Estimation of Hardy--Weinberg equilibrium was measured through $\chi 2$ test in PopGene software version 3.2. Population genetics indicators such as gene heterozygosity (He) and polymorphism information content (PIC) level were measured through established methods (Nei and Roychoudhury, 1974). The allelic frequencies of each SNP among cattle breeds or groups were compared by a $\chi 2$ test in Pop Gene software version 3.2.

Association analysis

A General Linear Model (GLM) (SPSS 24.0, Chicago, USA) was used for the association analysis between SNPs and selected body and carcass traits in QC. The statistical linear model for this analysis was the same as previous reports (Wei et al., 2018; Raza et al., 2020 b, c, d):

$$Y_{ijk} = \mu + G_i + A_i + A_k + e_{ijk}$$

where:

Y_{ijk} = trait value per individual,
μ = overall population mean per trait,
G_i = fixed effect associated with genotype,
A_i = fixed effect of age,
A_k = fixed effect due to the age of dam,
e_{ijk} = standard error.

The Bonferroni correction was used to adjust P values (Wei et al., 2018).

Results

Genetic diversity of four SNPs in six cattle populations

For the *c.*188G>A* SNP of *AKIRIN2*, the *g.231054C>T* SNP of *TTN*, the *g.1471620G>T* SNP of *EDG1* and the *g.70014208A>G* SNP of *MYBPC1*, the frequencies of the two alleles and the three genotypes of each of four SNPs in the MGC, MGG, QC, LX, WL and LL cattle populations are listed in Table 3, as are the genetic indices (Ho, He, n_e and PIC). No significant departures from the Hardy–Weinberg equilibrium at the 5% level were detected by any test for the four SNPs (Table 3). In this study, the LL population showed the lowest value of PIC in each of four SNPs compared to the other cattle populations.

Table 3. Genotypic frequencies, allelic frequencies and diversity parameters of four SNPs in six cattle populations

SNP	Breed*	Number	Genotypic frequency			Allelic frequency		Diversity parameter*				
								Ho	He	n_e	PIC*	χ^2 (HWE)
1	2	3	4			5		6	7	8	9	10
*c.*188G>A* (*AKIRIN2*)			*AA*	*AG*	*GG*	*A*	*G*					
	MGC	41	0.024	0.195	0.780	0.122	0.878	0.786	0.214	1.273	0.191	0.324
	MGG	50	0.140	0.460	0.400	0.370	0.630	0.534	0.466	1.873	0.358	0.009
	QC	350	0.051	0.343	0.606	0.223	0.777	0.654	0.346	1.530	0.286	0.036
	LX	24	0.000	0.167	0.780	0.083	0.917	0.847	0.153	1.180	0.141	0.198
	WL	50	0.020	0.220	0.760	0.130	0.870	0.774	0.226	1.292	0.201	0.038
	LL	50	0.000	0.000	1.000	0.000	1.000	1.000	0.000	1.000	0.000	–
g.231054C>T (*TTN*)			*TT*	*TC*	*CC*	*T*	*C*					
	MGC	41	0.000	0.122	0.878	0.061	0.939	0.885	0.115	1.129	0.185	0.173
	MGG	50	0.020	0.180	0.800	0.110	0.890	0.804	0.196	1.243	0.282	0.326
	QC	350	0.017	0.249	0.734	0.141	0.859	0.757	0.243	1.321	0.213	0.194
	LX	24	0.000	0.125	0.878	0.063	0.938	0.883	0.117	1.133	0.240	0.107
	WL	50	0.000	0.060	0.940	0.030	0.970	0.942	0.058	1.062	0.090	0.048
	LL	50	0.000	0.000	1.000	0.000	1.000	1.000	0.000	1.000	0.000	–
g.42041062G>T (*EDG1*)			*TT*	*GT*	*GG*	*T*	*G*					
	MGC	41	0.000	0.146	0.854	0.073	0.927	0.864	0.136	1.157	0.126	0.256
	MGG	50	0.000	0.180	0.820	0.090	0.910	0.836	0.164	1.196	0.150	0.489
	QC	350	0.034	0.237	0.729	0.153	0.847	0.741	0.259	1.349	0.226	2.489
	LX	24	0.000	0.042	0.854	0.021	0.979	0.959	0.041	1.043	0.040	0.011
	WL	50	0.000	0.060	0.940	0.030	0.970	0.942	0.058	1.062	0.057	0.048
	LL	50	0.000	0.020	0.980	0.010	0.990	0.980	0.020	1.020	0.020	0.005

Table 3 – contd.

1	2	3	4			5		6	7	8	9	10
g.70014208A>G (*MYBPC1*)			*GG*	*GA*	*AA*	*G*	*A*					
	MGC	41	0.829	0.146	0.024	0.902	0.098	0.824	0.176	1.214	0.161	1.170
	MGG	50	0.820	0.180	0.000	0.910	0.090	0.836	0.164	1.196	0.150	0.489
	QC	350	0.831	0.151	0.017	0.907	0.093	0.832	0.168	1.203	0.154	3.581
	LX	24	0.917	0.083	0.024	0.958	0.042	0.920	0.080	1.087	0.077	0.045
	WL	50	0.940	0.060	0.000	0.970	0.030	0.942	0.058	1.062	0.057	0.048
	LL	50	0.980	0.020	0.000	0.990	0.010	0.980	0.020	1.020	0.020	0.005

*QC, Qinchuan; LX, Luxi; MGC, Mongolia cattle population (Inner Mongolia Autonomous Region of China); MGG, Mongolia cattle population (Mongolia); WL, Wuling; LL, Longlin.

*Ho, observed heterozygosity; He, expected heterozygosity; n_e, effective allele numbers; PIC, polymorphism information content; HWE, Hardy–Weinberg equilibrium.

*The classification was conducted according to the PIC values (PIC<0.25, low polymorphism; 0.25<PIC<0.5, moderate polymorphism; and PIC>0.5, high polymorphism).

Table 4. Association of four SNPs with growth traits in Qinchuan cattle

SNP	Genotype (No.)	Growth traits*						
		BL (cm)	WH (cm)	HH (cm)	HW (cm)	RL (cm)	CD (cm)	CC (cm)
*c.*188G>A* (*AKIRIN2*)	*GG* (212)	133.24±0.90 a	120.53±0.61	123.33±0.55	38.24±0.41 Aa	41.68±0.32	58.02±0.43 a	161.33±1.22 a
	GA (120)	134.60±1.18 b	121.67±0.84	123.89±0.72	38.42±0.55 B	41.98±0.40	59.30±0.66	164.04±1.68 b
	AA (18)	141.03±3.89 b	124.19±2.25	126.64±2.06	41.36±1.77 b	43.53±1.17	62.69±2.38 b	169.06±4.50
g.231054C>T (*TTN*)	*CC* (257)	133.78±0.82	120.41±0.55 a	123.22±0.48	38.17±0.38	41.75±0.27	58.19±0.42 a	161.21±1.10 a
	CT (87)	134.28±1.49	122.62±1.06 b	124.71±0.91	39.03±0.67	42.05±0.57	59.90±0.80 b	165.95±2.11 b
g.42041062G>T (*EDG1*)	*GG* (255)	134.77±0.82	121.28±0.54	123.89±0.47	38.87±0.35 a	41.98±0.28	58.83±0.42	163.52±1.09
	GT (83)	131.37±1.49	120.13±1.12	122.73±1.02	37.02±0.77 b	41.42±0.55	58.23±0.85	159.25±2.24
	TT (12)	138.96±3.67	124.33±2.27	126.08±1.98	39.83±1.80	42.75±1.44	59.13±1.78	167.83±4.87
g.70014208A>G (*MYBPC1*)	*GG* (291)	135.19±0.80 A	121.71±0.53 a	124.11±0.47 a	38.89±0.35 A	42.19±0.27 A	59.04±0.41 a	163.93±1.07
	GA (53)	128.17±1.41 B	118.25±1.17 b	121.57±1.03 b	35.97±0.82 B	40.22±0.54 B	56.85±0.91 b	156.16±2.31

*BL: body length; WH: wither height; HH: hip height; HW: hip width; RL: rump length; CD: chest depth; CC: chest circumference.
*Values are shown as the means ± standard error.
*Values with different letters are significantly different at $P<0.05$ (a, b) and $P<0.01$ (A, B) after Bonferroni correction.

Associations between four SNPs and growth traits in Qinchuan cattle

The effects of the *c.*188G>A* SNP of *AKIRIN2*, the *g.231054C>T* SNP of *TTN*, the *g.1471620G>T* SNP of *EDG1* and the *g.70014208A>G* SNP of *MYBPC1* on growth traits were analyzed in 350 QC population (Table 4). For the *c.*188G>A* SNP in *AKIRIN2*, the individuals with *AA* and *GA* genotypes had significantly longer body length than the individuals with *GG* genotype (P<0.05); the individuals with *AA* and *GA* had significantly greater hip width than the individuals with *GG* (P<0.05, P<0.001, respectively); and the genotypes of the *c.*188G>A* SNP also had statistically significant effect on chest depth (P<0.05) and chest circumference (P<0.05) (Table 4). For the *g.231054C>T* SNP in *TTN*, there were only six cattle with the *TT* genotype, therefore, their associations and effects could not be reliably estimated and they were excluded from the analysis. The individuals with *CT* genotype had significantly greater wither height (P<0.05), chest depth (P<0.05) and chest circumference (P<0.05) compared with the individuals with *CC* genotype (Table 4). For the *g.1471620G>T* SNP in *EDG1*, there were significant differences between *GG* and *GT* genotype of hip width (P<0.05), whereas no association was detected in the other growth traits (Table 4). For the *g.70014208A>G* SNP in *MYBPC1*, the only six cattle with *AA* genotype were excluded from the analysis. Thus, the animals with *GG* homozygotes exhibited significantly greater body length (P<0.001), wither height (P<0.05), hip height (P<0.05), hip width (P<0.01), rump length (P<0.01) and chest depth (P<0.05) compared to the animals with *GA* heterozygotes (Table 4).

Table 5. Association of four SNPs with carcass traits in Qinchuan cattle

SNP	Genotype (No.)	Carcass traits*		
		BFT (cm)	ULMA (cm^2)	ULMD (cm)
*c.*188G>A* (*AKIRIN2*)	*GG* (212)	0.89±0.02	47.12±1.14	4.51±1.14
	GA (120)	0.89±0.03	47.44±1.34	4.53±1.50
	AA (18)	1.05±0.12	47.57±3.33	4.71±3.43
g.231054C>T (*TTN*)	*CC* (257)	45.53±0.97 A	0.88±0.02	4.50±0.08
	CT (87)	51.09±1.66 B	0.94±0.03	4.60±0.15
g.42041062G>T (*EDG1*)	*GG* (255)	0.89±0.02 a	44.99±0.94 Aa	4.45±1.19
	GT (83)	0.88±0.03 a	52.93±1.69 B	4.77±1.68
	TT (12)	1.13±0.16 b	56.14±6.19 b	4.53±1.29
g.70014208A>G (*MYBPC1*)	*GG* (291)	0.91±0.02	47.37±0.95	4.60±0.22 A
	GA (53)	0.84±0.04	47.83±1.97	4.09±0.07 B

*BFT: back fat thickness; ULMA: ultrasound longissimus muscle area; ULMD: ultrasound longissimus muscle depth.

*Values are shown as the means ± standard error.

*Values with different letters are significantly different at P<0.05 (a, b) and P<0.01 (A, B) after Bonferroni correction.

Associations between four SNPs and carcass traits in Qinchuan cattle

The results of association between the *c.*188G>A* SNP of *AKIRIN2*, the *g.231054C>T* SNP of *TTN*, the *g.1471620G>T* SNP of *EDG1* and the *g.70014208A>G* SNP of *MYBPC1* and carcass traits in 350 QC are shown in Ta-

ble 5. For the *c.*188G>A* SNP in *AKIRIN2*, no significant effect on the back fat thickness, ultrasound longissimus muscle area and ultrasound longissimus muscle depth was detected in QC (Table 5). For the *g.231054C>T* SNP in *TTN*, the SNP genotype had the statistically significant effect on the back fat thickness (P<0.01), but not for ultrasound longissimus muscle area and ultrasound longissimus muscle depth in QC (Table 5). For the *g.70014208A>G* SNP in *MYBPC1*, the ultrasound longissimus muscle depth of the *GA* heterozygotes was significantly greater than that of the *GG* homozygotes (P<0.001), but not for back fat thickness and ultrasound longissimus muscle area in QC cattle (Table 5). In addition, at the *g.1471620G>T* locus of *EDG1*, the back fat thickness of the *TT* homozygotes was significantly thinner than those of the *GT* heterozygotes and *GG* homozygotes (P<0.05). The ultrasound longissimus muscle area of the *TT* homozygotes was significantly larger than that of the *GG* homozygotes (P<0.05), as well as that of the *GT* heterozygotes was significantly larger than that of the *GG* homozygotes (P<0.001) (Table 5).

Table 6. Statistical significance for differences in the allele frequencies of the four SNPs among the six groups of cattle populations

SNP	Group	Group				
		Central China	South China	Japanese cattle*[1]	European cattle*[1]	Korean native cattle*[2]
*c.*188G>A* SNP (*AKIRIN2*)	North China	n.s.	***	**	n.s.	***
	Central China		***	***	n.s.	***
	South China			***	***	***
	Japanese cattle				***	n.s.
	European cattle					***
g.231054C>T SNP (*TTN*)	North China	n.s.	**	***	***	–
	Central China		***	***	***	–
	South China			***	**	–
	Japanese cattle				***	–
g.1471620G>T SNP (*EDG1*)	North China	*	**	***	***	–
	Central China		***	***	***	–
	South China			***	*	–
	Japanese cattle				***	–
g.70014208A>G SNP (*MYBPC1*)	North China	n.s.	**	***	***	–
	Central China		***	***	***	–
	South China			***	***	–
	Japanese cattle				***	–

*n.s.: non-significant; * P<0.05; ** P<0.01; *** P<0.001.

*[1]The data of the *g.1471620G>T* SNP (*EDG1*), *g.70014208A>G* SNP (*MYBPC1*), *c.*188G>A* SNP (*AKIRIN2*) and *g.231054C>T* SNP (*TTN*) in Japanese and European cattle breeds were referred from Watanabe et al., 2010, 2011; Tong et al., 2014 b.

*[2]The data of the *c.*188G>A* SNP (*AKIRIN2*) in Korean native cattle was referred from Kim et al., 2013.

Statistical comparisons of allele frequencies among six cattle groups

To further analyze the distribution of the well-characterized allele of each of the four SNPs in the experimental cattle populations based on the different genetic background, the MGC, MGG, QC, LX, WL and LL of this study as well as the JB,

JBR, JSH, HOL, BS and KN were divided into six groups which included North China (NC, including MGC and MGG), Central China (CC, including QC and LX), South China (SC, including WL and LL) (CNCAGR, 2011), Japanese cattle group (JG, including JB, JBR and JSH), European cattle group (EG, including HOL and BS), and KN (Table 6). The distribution of the well-characterized allele frequency of each SNP in the cattle populations based on the different genetic background are shown in Figure 1. At the *c.*188G>A* locus in *AKIRIN2*, the well-characterized *A* allele frequency in the JG and KN was obviously higher than the other cattle groups (Table 6). At the *g.231054C>T* locus in *TTN*, the well-characterized *T* allele frequency in the JG was significantly higher than the other cattle groups ($P<0.001$, Table 6). At the *g.1471620G>T* locus in *EDG1*, the well-characterized *T* allele frequency in the JG was significantly higher than the other cattle groups ($P<0.001$, Table 6). On the contrary, the distribution of the well-characterized *G* allele frequency of the *g.70014208A>G* SNP in *MYBPC1* was significantly higher in NC, CC and SC than the JG and EG ($P<0.001$, Table 6). In addition, the well-characterized *T* allele of the *g.231054C>T* SNP was almost absent in the SC and EG, the same to the well-characterized *T* allele of the *g.1471620G>T* SNP in the SC and EG, as well as the well-characterized *G* allele frequency of the *g.70014208A>G* SNP in the EG. The χ^2 tests for different distribution of allele frequencies of the *c.*188G>A* SNP in *AKIRIN2*, the *g.231054C>T* SNP in *TTN*, the *g.1471620G>T* SNP in *EDG1* and the *g.70014208A>G* SNP in *MYBPC1* genes between any two cattle groups are listed in Tables S1–4.

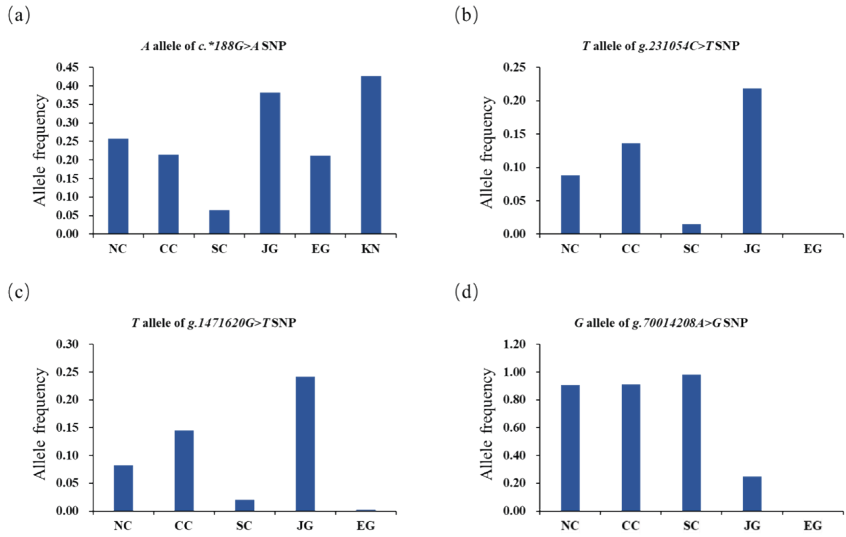

Figure 1. Distribution of the well-characterized allele of each SNP in the cattle populations based on the different genetic background. (a) The *A* allele of *c.*188G>A* SNP (b) The *T* allele of *g.231054C>T* SNP (c) The *T* allele of *g.1471620G>T* SNP (d) The *G* allele of *g.70014208A>G* SNP. NC: North China; CC: Central China; SC: South China; JG: Japanese cattle group; EG: European cattle group; KN: Korean native cattle

Discussion

The *AKIRIN2*, *TTN*, *EDG1* and *MYBPC1* genes showed different expression levels in the longissimus muscle between JB and HOL (Sasaki et al., 2006 a). These genes are located within genomic regions of QTLs for carcass and growth traits in JB, Angus and some crossbred populations (Takasuga et al., 2007; McClure et al., 2010; Casas et al., 2003; Mateescu et al., 2017; Casas et al., 2001; Boichard et al., 2003; Peters et al., 2012). The *c.*188G>A* SNP in the 3'UTR of *AKIRIN2* showed associations with marbling score in JB (Sasaki et al., 2009) as well as marbling score and longissimus muscle area in KN (Kim et al., 2013). The proposed function of Akirins is as a transcription factor required for NF-jB-dependent gene expression in Drosophila and mice, and in the regulation of the innate immune response in Drosophila (Goto et al., 2008; Galindo et al., 2009). We speculate that the *c.*188G>A* SNP might affect mRNA stability to decrease the expression level of *AKIRIN2*, resulting in high growth performance in QC. The *g.231054C>T* SNP in the promoter region of *TTN* showed associations with marbling score and longissimus muscle area in JB (Yamada et al., 2009 a, 2011). Since *TTN* is known to be involved in myofibrillogenesis (Itoh-Satoh et al., 2002), we can hypothesize that the *g.231054C>T* SNP in the promoter region might have an impact on *TTN* expression and also growth performance by affecting *TTN* promoter activity in QC. The *g.1471620G>T* SNP in the promoter region of *EDG1* showed association with marbling score in JB (Yamada et al., 2009 b), simultaneously one other SNP in *EDG1* had effects on marbling score, subcutaneous fat thickness, carcass weight, longissimus muscle area and rib thickness (Yamada et al., 2009 c; Sukegawa et al., 2010). The *EDG1* is known to be involved in blood vessel formation (Liu et al., 2000), The *g.1471620G>T* SNP might have an impact on *EDG1* expression and also back fat thickness, ultrasound longissimus muscle area by affecting *EDG1* promoter activity in QC. The *g.70014208A>G* SNP in the promoter region of *MYBPC1* had effects on marbling score and longissimus muscle area (Tong et al., 2014 a, 2015). The *MYBPC1* interacts with muscle-type creatine kinase, potentially allowing it to regulate energy homeostasis during muscle contraction by coupling to the myofibril (Chen et al., 2011). Thus, the increase of the *MYBPC1* expression level might lead to high growth performance through enhancing muscle satellite cell proliferation. We suggest that the *g.70014208A>G* SNP might have an impact on the *MYBPC1* expression, and also growth performance by affecting the *MYBPC1* promoter activity in QC.

Around the second century A.D., cattle migrated from North Asian continent via the Korean peninsula to Japan (Mukai et al., 1989). In Japanese cattle, both genetic (Namikawa, 1980) and morphological (Ogawa et al., 1989) studies have illustrated that native Japanese cattle are *Bos taurus* and are representatives of the "Turano-Mongolian" type (Felius, 1995). The Korean native cattle (Hanwoo), is a cattle breed that is native to the Korean peninsula and the Japanese islands, which is considered to belong to the *Bos taurus* (Mannen et al., 1998, 2004; Seung et al., 2004). Actually, the JB has been subjected to strong selection for high marbling over the last 50 years, but not in other breeds such as JBR and JSH, as well as all Korean indigenous cattle

breeds are just used for beef meat production (Sasaki et al., 2006 b) and consumer demands are driving efforts to increase meat production and produce higher quality meat in Korea (Han et al., 2011). Unlike them, the growth performance is regarded as the major breeding goal in most breeds of Chinese indigenous cattle. In this study, the frequencies of marbling-related *A* allele (in the *c.*188G>A* SNP of *AKIRIN2*) in the JB and KN, *T* allele (in the *g.231054C>T* SNP of *TTN*) in JB and *T* allele (in the *g.1471620G>T* SNP of *EDG1*) in JB were significantly higher than in Chinese cattle breeds (Tables S1–S4). The probable reason could be the breeding for high marbling in JB and KN cattle breeds. Interestingly and conversely, the well-characterized *G* allele (in the *g.70014208A>G* SNP of *MYBPC1*) was markedly higher in Chinese cattle breeds than JB (Table S4). Moreover, the *G* allele (in the *g.70014208A>G* SNP of *MYBPC1*) was almost null in JBR and JSH; on the contrary, the *G* allele was almost full in WL and LL breeds of CC (Table 3), likely due to genetic background. In addition, the PIC of each SNPs in HOL and BS of EG was related low or null, maybe due to the breeding aim for dairy-related traits in HOL and BS. We noted that well-known cattle breeds such as Angus and Shorthorn should be tested to explore the distribution of the well-characterized alleles in European beef cattle in the future study.

Recently, China cattle beef industry is growing rapidly to meet the meat demand of large population. Although a large number of molecular markers has been identified for breeding purpose, still more research is needed to explore more useful molecular markers for the cattle breed improvement programs (Tong et al., 2017). In the present study, association analysis showed effects of four SNPs on growth and carcass traits including body length, wither height, hip height, hip width, rump length, chest depth, chest circumference, back fat thickness, ultrasound longissimus muscle area and ultrasound longissimus muscle depth in Chinese QC cattle. However, future research is needed to confirm their effects in larger cattle populations.

Conclusion

The results of this study suggest that the *c.*188G>A* SNP of *AKIRIN2*, the *g.231054C>T* SNP of *TTN*, the *g.1471620G>T* SNP of *EDG1* and the *g.70014208A>G* SNP of *MYBPC1* genes might be useful as a specific DNA marker for growth and carcass traits in Chinese QC cattle.

Conflict of interest

The authors declare that they have no conflict of interest.

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Table S1. Statistical significance for differences in the A allele frequency of c.*188G>A SNP among 12 cattle populations

Breed*	LX	MGC	MGG	WL	LL	JB*[1]	JBR*[1]	JSH*[1]	HOL*[1]	BS*[1]	KN*[2]
QC	*	*	**	*	***	***	***	***	n.s.	n.s.	***
LX		n.s.	***	n.s.	**	***	***	n.s.	*	*	***
MGC			***	n.s.	***	***	***	**	n.s.	n.s.	***
MGG				***	***	*	**	***	**	**	n.s.
WL					***	***	***	***	n.s.	n.s.	***
LL						***	***	n.s.	***	***	***
JB							n.s.	***	***	***	n.s.
JBR								***	***	***	***
JSH									***	***	***
HOL										n.s.	***
BS											***

*QC: Qinchuan; LX: Luxi; MGC: Mongolia cattle population (Inner Mongolia Autonomous Region of China); MGG: Mongolia cattle population (Mongolia); WL: Wuling; LL: Longlin; JB: Japanese Black; JBR: Japanese Brown; JSH: Japanese Short Horn; HOL: Holstein; BS: Brown Swiss; KN: Korean native cattle.

*n.s.: non-significant; * P<0.05; ** P<0.01; *** P<0.001.

*[1]The data of the *c.*188G>A* SNP (*AKIRIN2*) in Japanese and European cattle breeds were referred from Watanabe et al., 2011.

*[2]The data of the *c.*188G>A* SNP (*AKIRIN2*) in Korean native cattle was referred from Kim et al., 2013.

Table S2. Statistical significance for differences in the *T* allele frequency of g.231054C>T SNP among 11 cattle populations

Breed	LX	MGC	MGG	WL	LL	JB*[1]	JBR*[1]	JSH*[1]	HOL*[1]	BS*[1]
QC	n.s.	*	n.s.	**	***	***	***	n.s.	***	***
LX		n.s.	n.s.	n.s.	*	**	**	n.s.	***	***
MGC			n.s.	n.s.	*	***	***	n.s.	***	***
MGG				*	***	**	**	n.s.	***	***
WL					n.s.	***	***	n.s.	**	**
LL						***	***	**	–	–
JB							n.s.	***	***	***
JBR								***	***	***
JSH									***	***
HOL										–

*QC: Qinchuan; LX: Luxi; MGC: Mongolia cattle population (Inner Mongolia Autonomous Region of China); MGG: Mongolia cattle population (Mongolia); WL: Wuling; LL: Longlin; JB: Japanese Black; JBR: Japanese Brown; JSH: Japanese Short Horn; HOL: Holstein; BS: Brown Swiss.

*n.s.: non-significant; * P<0.05; ** P<0.01; *** P<0.001.

*[1]The data of the *g.231054C>T* SNP (*TTN*) in Japanese and European cattle breeds were referred from Watanabe et al., 2011.

Table S3. Statistical significance for differences in the *T* allele frequency of g.1471620G>T SNP among 11 cattle populations

Breed*	LX	MGC	MMG	WL	LL	JB*[1]	JBR*[1]	JSH*[1]	HOL*[1]	BS*[1]
QC	*	n.s.	n.s.	***	***	***	***	***	***	***
LX		n.s.	n.s.	n.s.	n.s.	***	n.s.	n.s.	*	n.s.
MGC			n.s.	n.s.	*	***	n.s.	n.s.	***	***
MGG				n.s.	**	***	n.s.	*	***	***
WL					n.s.	***	n.s.	n.s.	**	n.s.
LL						***	n.s.	n.s.	n.s.	n.s.
JB							***	***	***	***
JBR								n.s.	**	*
JSH									*	n.s.
HOL										n.s.

*QC: Qinchuan; LX: Luxi; MGC: Mongolia cattle population (Inner Mongolia Autonomous Region of China); MGG: Mongolia cattle population (Mongolia); WL: Wuling; LL: Longlin; JB: Japanese Black; JBR: Japanese Brown; JSH: Japanese Short Horn; HOL: Holstein; BS: Brown Swiss.

*n.s.: non-significant; * P<0.05; ** P<0.01; *** P<0.001.

*[1]The data of the *g.1471620G>T* SNP (*EDG1*) in Japanese and European cattle breeds were referred from Watanabe et al., 2010.

Table S4. Statistical significance for differences in the *G* allele frequency of *g.70014208A>G* SNP among 11 cattle populations

Breed*	LX	MGC	MGG	WL	LL	JB*[1]	JBR*[1]	JSH*[1]	HOL*[1]	BS*[1]
QC	n.s.	n.s.	n.s.	*	**	***	***	***	***	***
LX		n.s.	n.s.	n.s.	n.s.	***	***	***	***	***
MGC			n.s.	n.s.	**	***	***	***	***	***
MGG				n.s.	**	***	***	***	***	***
WL					n.s.	***	***	***	***	***
LL						***	***	***	***	***
JB							***	***	***	***
JBR								n.s.	n.s.	–
JSH									n.s.	n.s.
HOL										n.s.

*QC: Qinchuan; LX: Luxi; MGC: Mongolia cattle population (Inner Mongolia Autonomous Region of China); MGG: Mongolia cattle population (Mongolia); WL: Wuling; LL: Longlin; JB: Japanese Black; JBR: Japanese Brown; JSH: Japanese Short Horn; HOL: Holstein; BS: Brown Swiss.

*n.s.: non-significant; * P<0.05; ** P<0.01; *** P<0.001.

*[1]The data of the *g.70014208A>G* SNP (*MYBPC1*) in Japanese and European cattle breeds were referred from Tong et al., 2014 b.

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