ORIGINAL ARTICLE

Interval mapping of growth quantitative trait loci in Japanese Black beef cattle using microsatellite DNA markers and half-sib regression analysis

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ABSTRACT

A confirmatory scan for the regions of bovine chromosome 1 segregating the quantitative trait loci (QTL) influencing birth-weight, weaning weight, yearling weight, and preweaning and postweaning average daily gains was performed by genotyping half-sib progeny of four Japanese Black sires using microsatellite DNA markers. Data were analyzed by generating an *F*-statistic every 1 cM on a linkage map by the regression of phenotype on the probabilities of inheriting an allele from the sire after adjusting for the fixed effects of sire, sex, parity and season of birth as well as age as a covariate. Permutation tests at chromosome-wide significance thresholds were carried out over 10 000 iterations. A significant QTL for birth-weight at 114 cM was detected in the sire 2 family. This identification of a birthweight QTL in Japanese Black cattle may be useful for the implementation of marker-assisted selection.

KEYWORDS: growth, Japanese Black cattle, microsatellite markers, quantitative trait loci (QTL).

INTRODUCTION

Breeding beef bulls are evaluated by their growth rate and yearling weight because of the positive correlation between growth and carcass traits (Baik *et al.* 2003; Koch *et al.* 2004). Japanese Black is the main beef cattle breed in Japan and is revered as a producer of high-quality meat. The growth of this breed, as reflected by liveweight changes from birth to yearling age, is important for the early attainment of slaughter weight. Identifying quantitative trait loci (QTL) has the potential to significantly increase the rate of genetic improvement through implementation of marker-assisted selection (Macneil & Grosz 2002). For traits that are difficult or expensive to measure, are lowly heritable, occur late in life or are determined postmortem, marker-assisted selection may increase the rate of response relative to selection based on estimated breeding

value alone (Davis & DeNise 1998). Therefore, selection indices that include QTL with accurately estimated effects on growth traits could reduce the amount of lengthy and costly data collection by providing a means of genetic evaluation early in the life cycle.

Microsatellite DNA markers on genetic maps are used to identify inheritance patterns of linked segments of the genome in structured pedigree populations. Significant associations of the marker allele with the phenotype of interest suggest linkage of

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the markers to QTL. The detection and mapping of QTL for birthweight, liveweight, growth and carcass traits in paternal half-sib families of Charolais $\times$ Brahman, Brahman, Piedmontese, Belgian Blue and Beefbooster cattle has been reported (Davis *et al.* 1998; Stone *et al.* 1999; Casas *et al.* 2000, 2003; Li *et al.* 2002, 2004a,b). The mapping of QTL is the first step towards the identification of genes and causal polymorphisms for traits of importance in agriculture (Seaton *et al.* 2002). There are ongoing collaborative studies on QTL mapping for carcass traits in Japanese Black cattle between the Livestock Improvement Association, Shirakawa Institute of Animal Genetics and 21 Prefectures in Japan (Mizoguchi 1998) and some preliminary results have been reported at conferences. A number of simulated and theoretical studies on marker-assisted selection (Saito & Iwaisaki 1996, 1997a,b; Saito *et al.* 1998), as well as mathematical modeling of QTL cluster effects in granddaughter design, multigroup and outbred populations (Matsuda & Iwaisaki 2000, 2001a,b,c), have been published. Therefore in the present study, we report for the first time, the results of QTL analysis for growth traits in 112 half-sib progeny from four Japanese Black sires. Preliminary genome-wide scanning in our laboratory using only 30 animals (unpublished data) had suggested *Bos taurus* autosomes (BTA) 1, 2 and 5 as chromosomes containing segregating QTL that significantly influenced the growth traits in Japanese Black cattle. Stone *et al.* (1999) had also reported a significant QTL affecting birthweight on BTA1 in Brahman $\times$ Hereford cattle. More recently, Kim *et al.* (2003) detected a significant QTL for yearling weight on bovine chromosome one (BTA1) in Angus $\times$ Brahman crosses. Comparative mammalian genomics reveal that BTA1 is equivalent to the human chromosome 3 (<http://bos.cvm.tamu.edu/htmls/rhbov1.html>), which has been demonstrated to harbour growth-regulating genes such as the growth hormone secretagogue receptor, also known as *ghrelin* (Shuto *et al.* 2002; Choi *et al.* 2003; Hosoda *et al.* 2003), *glycogenin* (Mu *et al.* 2001) and *Pit-1* (Ohta *et al.* 1992; Hendriks-Stegeman *et al.* 2001). It is therefore justifiable to focus on BTA 1 in the scan for growth QTL in Japanese Black cattle. Our objective was to conduct a confirmatory scan for segregating QTL on BTA1 that influence bodyweight at birth, weaning and yearling age, and average daily gain before and after weaning by genotyping more Japanese Black cattle.

MATERIALS AND METHODS

Animals and management

One hundred and twelve paternal half-sib progeny of four Japanese Black sires produced by artificial insemination at the Department of Livestock and Grassland Science, National Agricultural Research Center for Western Region, Oda, Shimane Prefecture, Japan, were genotyped. Routine management of the animals involved recording of weight at birth and monthly thereafter, until 18 months of age. Calves were allowed to suckle their dams in addition to being fed 1.5 kg/day per head of concentrate and 1 kg/day per head of corn silage until 5 months of age when they were weaned. After weaning, they were moved to the grower's barn and continued to be raised on concentrates (37% corn grain, 39% rice bran, 17% soybean meal, 7% minerals) and corn silage until 10 months of age. Between 10 and 18 months of age, they were moved to another barn and fed intensively. The proportions of the ration on a dry matter basis were 61% corn grain, 34% soybean and corn gluten meal, 2% bran and 3% minerals. For every 20 kg bag, this ration provided an estimated 21% crude protein, 3.5% crude fat, 5% crude fiber, 7% ash, 0.6% calcium, 0.40% phosphate and a total digestible nutrients of 77%. From 18 to 24 months of age, breeding females were returned to the calving barn and the steers were moved to the fattening barn where they were raised primarily on "Mosa meal", a specially formulated fattening ration containing 77% corn and rye grain, 10.5% wheat and rice bran, 9% soybean oil meal and 3.5% mineral supplement. At all ages, routine veterinary vaccinations and health checks were carried out.

Extraction of genomic DNA

Following the method of Sambrook *et al.* (1989) and described in detail elsewhere (Malau-Aduli *et al.* 2003), genomic DNA was extracted and prepared from blood leukocytes and sperm.

Polymerase chain reaction (PCR)

The PCR premix (13 μ L) comprised: 10.55 μ L of distilled water, 1.04 μ L of 2.5 mmol/L dNTP mixture (Takara, Shiga, Japan), 1.3 μ L of 10 $\times$ buffer containing 15 mmol/L MgCl₂ and 0.11 μ L of 25 mmol/L of MgCl₂. A primer (12.5 pmol/ μ L) of the microsatellite DNA markers, each of which was labeled with one of three different fluorescent labels, FAM, HEX and TET (supplied by the Shirakawa Institute of Animal

Genetics, Fukushima, Japan, and based on the bovine genetic map at the US Meat Animal Research Center (Kappes *et al.* 1997; <http://sol.marc.usda.gov>) was added to the PCR premix. Genomic DNA (1 µL; 20 ng/µL) was added, followed by 0.5 µL of Taq polymerase enzyme (0.75 units/µL) containing 50% glycerol (Takara). The PCR plates were hotplate-sealed and subjected to PCR in a DNA thermal cycler. The annealing temperature settings were 50°C, 55°C and 60°C.

Genotyping

Multiplex genotyping was carried out. Prior to genotyping, the PCR products were mixed with the markers, which could be genotyped simultaneously in combinations of 4 µL of HEX, 1 µL of FAM and 1 µL of TET. Next, 0.8 µL of the mixed PCR products was added to 4.5 µL of DNA size marker, centrifuged for 1 min at 120 *g* and denatured using the PCR machine at a denaturing temperature of 94°C for 9 min. The denatured products were subjected to electrophoresis and genotyping in an ABI 377 DNA Sequencer. A total of 82 informative microsatellite DNA markers were used for the genotyping (Table 1).

Traits analyzed

Offspring of the four sires born between 1997 and 2002 were evaluated for growth traits. Birthweight (BWT), weaning weight (WT6) and yearling weight (WT12) were measured in kilograms, and the preweaning average daily gain (PREWADG) and postweaning average daily gain (POSTADG) were computed in kg/day (SAS Institute 2002).

QTL analysis

We adopted the methods of Haley and Knott (1992), Knott *et al.* (1996) and De Koning *et al.* (1998, 2001) for the detection and mapping of QTL in half-sib populations using least squares simple regression. We used the *QTL Express* computer program with a web-based user interface (<http://qtl.cap.ed.ac.uk/>) developed by Seaton *et al.* (2002) and based on the methods of the previously mentioned researchers for the QTL analysis. The half-sib model of *QTL Express* run within and across sires, implemented the analysis in a two-step procedure. First, microsatellite DNA marker data on progeny and their common parent (sire) were combined in a multipoint approach to calculate the

Table 1 Informative microsatellite DNA markers used for genotyping the five Japanese Black cattle families and their relative map positions (cM)*

Family	Marker	Position	Family	Marker	Position	Family	Marker	Position	Family	Marker	Position
1	BMS1928	6.9	2	BM8139	8.2	3	BMS2321	14.0	4	BMS1928	6.9
1	BMS711	21.3	2	TGLA57	46.2	3	ILSTS104	28.2	4	BMS711	21.3
1	ILSTS104	28.2	2	BMS4012	51.0	3	BMS4002	47.9	4	TGLA57	46.2
1	MB055	32.0	2	BMS4013	61.3	3	BMS4012	51.0	4	BMS4035	55.0
1	TGLA57	46.2	2	BMS4001	64.7	3	BMS4035	55.0	4	BMS4029	61.3
1	BMS4012	51.0	2	BM9019	67.5	3	RME36	63.0	4	BM9019	67.5
1	BMS4035	55.0	2	BL26-1	77.7	3	BM8246	76.2	4	BMS4008	71.7
1	RM326	55.6	2	BMS4006	79.4	3	BMS119	88.6	4	BMS4048	76.2
1	RME36	63.0	2	URB038	80.6	3	BMS4019	98.8	4	URB038	80.6
1	INRA049	67.5	2	MCM130	83.3	3	UWCA46	113.8	4	BMS4010	87.1
1	BM65O6	69.2	2	BMS4010	87.1	3	BMS599	125.8	4	BM864	88.2
1	URB038	80.6	2	BM864	88.2				4	BMS1170	92.8
1	BMS4052	94.6	2	BMS1170	92.8				4	BMS4019	98.8
1	BMS4028	95.6	2	BMS4028	95.6				4	BMS4011	102.1
1	BMS4040	98.8	2	BMS4019	98.8				4	BMS4049	114.3
1	BMS1789	100.9	2	BMS1789	100.9				4	BMS918	118.1
1	BMS4044	128.7	2	BMS1939	104.1				4	BMS599	125.8
1	BMS2263	135.1	2	BMS4039	108.3				4	BMS4044	128.7
			2	BM3205	113.8				4	BMS922	135.5
			2	BMS599	125.8						
			2	BMS4043	128.7						
			2	BMS2263	135.1						
			2	BMS4014	135.5						
Total	18			23			11			19	

*Based on the bovine genetic map at the US Meat Animal Research Center (Kappes *et al.* 1997; <http://sol.marc.usda.gov>).

probabilities of inheriting allele 1 or 2 from the sire at specific chromosomal intervals. These probabilities were combined into coefficients with values between 0.0 and 1.0. Second, the phenotypic data on progeny were regressed on these coefficients in a within-common-parent regression analysis. A linear model containing the fixed effects of sire, sex, parity and season of birth, as well as age as a covariate, was fitted to the probability coefficients and phenotypic data. Appropriate *F*-statistic thresholds for a $P < 0.05$ chromosome-wide type 1 error rate were generated by permutation test as described by Churchill and Doerge (1994), Doerge and Churchill (1996) (and applied to other half-sib studies by Spelman *et al.* 1996 and Vilkki *et al.* 1997). In determining significant thresholds, the *QTL Express* software (Seaton *et al.* 2002) computed both the *F*-statistics and the *F*-threshold at $P < 0.05$ chromosome-wide level. QTL were classified as significant when the *F*-statistic exceeded the *F*-threshold indicating a marker-trait association. Finally, the bootstrap procedure of Visscher *et al.* (1996) was followed to estimate the confidence intervals of the QTL locations.

RESULTS

A scan for the chromosomal regions of BTA1 segregating the QTL influencing BWT, WT6, WT12, PREWADG and POSTADG was performed by genotyping paternal half-sib progeny of four Japanese Black sires. Table 1 shows the number of informative microsatellite markers, their intervals and positions across the four Japanese Black sires. In sires 1, 2, 3 and 4, 18, 23, 11 and 19 markers spanning 135.1, 135.5, 125.8 and 135.5 cM, respectively, were informative. The number of alleles ranged from a minimum of 3 to a maximum of 9.

Means and standard deviations of phenotypic data of the progeny across sires are shown in Table 2 and Table 3 shows the estimated regression coefficients of

sire QTL (additive/allele substitution) effects and estimated QTL locations corresponding to the peak of *F*-statistics, as well as chromosome-wide 5% thresholds and 95% confidence intervals for the growth traits across sires. A QTL at 114 cM between the markers BMS4039 and BM3205 in sire 2 achieved chromosome-wide significance ($P < 0.05$). No other chromosomal regions were shown to contain QTL effects that reached chromosome-wide significance. Figure 1 is a graphical depiction of the map of the *F*-statistics in the four sires.

DISCUSSION

The early attainment of slaughter weight in beef cattle hinges on the growth potential of calves. Thus, BWT, WT6, WT12, PREWADG and POSTADG are important traits for the beef industry. However, the strong, positive genetic correlation of 0.5–0.58 between BWT and WT12 (Grosz & MacNeil 2001) suggests that young breeding bulls selected for increased postnatal growth potential are expected to also sire calves having greater BWT, resulting in increased risk of dystocia. On the other hand, selection of sires with genetic potential to reduce BWT would concurrently sacrifice the growth potential of the calves. Therefore, identifying genes affecting pre- and postnatal growth coupled with marker-assisted selection, has the potential to overcome this genetic antagonism by allowing selection for growth during specific developmental stages. This in effect, decreases both the incidence of dystocia and economic loss inherent to calving difficulty while minimizing any coincident effect on postnatal growth (Grosz & MacNeil 2001).

The chromosome-wide significant ($P < 0.05$) QTL influencing BWT detected at 114 cM between the microsatellite DNA markers BMS4039 and BM3205 within the confidence interval spanning 50–119.5 cM in sire 2 (Table 3, Fig. 1) confirms the report of Stone *et al.* (1999) that BTA1 harbors putative QTL that

Table 2 Distribution of progeny across sires, sexes and the growth traits (means $\pm$ standard deviation) of Japanese Black cattle

Sire	Males	Females	Total	BWT (kg)	WT6 (kg)	WT12 (kg)	PREWADG (kg/day)	POSTWADG (kg/day)
1	22	18	40	34.73 $\pm$ 4.70	163.92 $\pm$ 21.73	300.85 $\pm$ 31.80	0.72 $\pm$ 0.11	0.76 $\pm$ 0.18
2	24	12	36	33.97 $\pm$ 4.75	172.62 $\pm$ 19.38	284.67 $\pm$ 34.14	0.77 $\pm$ 0.09	0.70 $\pm$ 0.19
3	10	9	19	28.68 $\pm$ 5.13	177.63 $\pm$ 20.52	299.95 $\pm$ 33.55	0.83 $\pm$ 0.10	0.62 $\pm$ 0.14
4	8	9	17	28.71 $\pm$ 3.32	176.71 $\pm$ 22.94	283.59 $\pm$ 29.12	0.82 $\pm$ 0.12	0.56 $\pm$ 0.20

BWT, birthweight; WT6, weaning weight; WT12, yearling weight; PREWADG, preweaning average daily gain; POSTADG, postweaning average daily gain.

Table 3 Regression coefficients of sire QTL (allele substitution) effects, estimated QTL locations and chromosome-wide *F*-statistics for growth traits of Japanese Black calves

Sire family	1	2	3	4
BWT				
$\beta \pm \text{SE}$	3.57 ± 1.96	3.70 ± 1.58	3.10 ± 2.43	-4.43 ± 1.24
Estimated QTL location (cM)	61	114*	47	111
<i>F</i> -statistic	3.32 NS	5.49 significant	1.63 NS	12.71 NS
Likelihood ratio	3.07	4.84	1.41	5.00
<i>F</i> -threshold ($P < 0.05$)	9.1	5.41	11.69	17.30
95%CI (cM)	40.0–119.0	50.0–119.5	40.0–125.0	40.0–126.0
WT6				
$\beta \pm \text{SE}$	-15.41 ± 9.40	15.59 ± 7.92	-15.97 ± 8.86	39.04 ± 11.33
Estimated QTL location (cM)	14	18	125	59
<i>F</i> -statistic	2.69 NS	3.87 NS	3.24 NS	11.87 NS
Likelihood ratio	2.51	3.51	2.62	4.82
<i>F</i> -threshold ($P < 0.05$)	9.11	10.19	13.59	30.22
95%CI (cM)	4.5–124.0	13.5–132.0	40.5–125.0	40.0–129.5
WT12				
$\beta \pm \text{SE}$	-21.40 ± 14.45	-34.82 ± 15.12	-18.49 ± 15.82	-55.35 ± 21.87
Estimated QTL location (cM)	14	48	52	115
<i>F</i> -statistic	2.19 NS	5.31 NS	1.37 NS	6.40 NS
Likelihood ratio	2.06	4.69	1.20	3.35
<i>F</i> -threshold ($P < 0.05$)	20.37	9.31	12.63	3.35
95%CI (cM)	6.5–122.0	40.0–132.0	40.0–123.0	42.0–131.0
PREWADG				
$\beta \pm \text{SE}$	-0.09 ± 0.05	0.07 ± 0.04	-0.09 ± 0.04	0.20 ± 0.06
Estimated QTL location (cM)	14	18	125	59
<i>F</i> -statistic	4.09 NS	3.61 NS	4.43 NS	11.70 NS
Likelihood ratio	3.72	3.29	3.40	4.79
<i>F</i> -threshold ($P < 0.05$)	4.25	4.43	12.94	32.16
95%CI (cM)	13.0–122.0	17.0–132.0	40.0–125.0	50.0–130.0
POSTADG				
$\beta \pm \text{SE}$	0.10 ± 0.09	-0.21 ± 0.10	-0.14 ± 0.06	0.18 ± 0.06
Estimated QTL location (cM)	82	27	29	77
<i>F</i> -statistic	1.25 NS	4.81 NS	5.20 NS	9.44 NS
Likelihood ratio	1.20	4.29	3.87	4.24
<i>F</i> -threshold ($P < 0.05$)	9.09	5.88	6.05	17.22
95%CI (cM)	20.0–128.0	20.0–132.0	20.0–125.0	20.0–132.0

*Chromosome-wide significance ($P < 0.05$) level QTL; 95%CI, 95% confidence intervals (based on the reduced model only).

BWT, birthweight; WT6, weaning weight; WT12, yearling weight; PREWADG, preweaning average daily gain; POSTADG, postweaning average daily gain; NS, not significant; QTL, quantitative trait loci; cM, centi-Morgan.

significantly increased BWT in Brahman $\times$ Hereford cattle. They also found that other growth-related QTL for WT6 and WT12 reached suggestive thresholds only on BTA1. Similarly, Kim *et al.* (2003) in their investigation of QTL for growth and beef carcass fatness traits in Angus $\times$ Brahman cattle, reported a significant QTL affecting WT12 in the interstitial region of BTA1. They also detected a total of 30 QTL with suggestive evidence for linkage and 4 other significant QTL on 19 chromosomes. Other researchers (Casas *et al.* 1998, 2000, 2003; Davis *et al.* 1998; Keele *et al.* 1999; Grosz & MacNeil 2001; MacNeil & Grosz 2002) have also investigated QTL affecting BWT, growth and carcass composition of beef cattle in the USA. Grosz and Mac-

Neil (2001) detected a QTL influencing BWT at the telomeric end of BTA2 located at 114 cM in the interval between BM2113 and OarFCB11 microsatellite markers. Davis *et al.* (1998) reported significant QTL effects on BWT in five chromosomes: BTA5, BTA6, BTA14, BTA18 and BTA21 located at 90, 48, 42, 116 and 4 cM, respectively. MacNeil and Grosz (2002) detected QTL for liveweight on BTA17 located at 52 cM. Casas *et al.* (2003) detected putative QTL for BWT on BTA1, BTA2 and BTA3, and for WT6 on BTA29. Genotyping work in our laboratory is currently focusing on BTA2 and BTA5 as part of the ongoing, long-term goal of whole genome-scanning of more Japanese Black cattle. The identification of a QTL

Fig. 1 Map of the F -statistics in the four Japanese Black sire families. In sire 2 family, there is a significant (bold line) $P < 0.05$ chromosome-wide threshold for birthweight.

in the present study indicates the presence of detectable segregation of alleles, hence a significant variation affecting an important trait (BWT) in Japanese Black cattle. This would be useful for the implementation of marker-assisted selection as an effective tool for the early attainment of slaughter weight in Wagyu cattle. Furthermore, this finding could pave the way for comparative candidate positional cloning in Japanese Black cattle using *ghrelin*, *glycogenin* or *Pit-1* as candidate genes. The prospect of subsequently isolating and characterizing the genes using single nucleotide polymorphisms appears quite promising.

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