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Research Article

Quantitative trait locus affecting birth weight on bovine chromosome 5 in a F_2 Gyr x Holstein population

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Abstract

Segregation between a genetic marker and a locus influencing a quantitative trait in a well delineated population is the basis for success in mapping quantitative trait loci (QTL). To detect bovine chromosome 5 (BTA5) birth weight QTL we genotyped 294 F_2 Gyr (*Bos indicus*) x Holstein (*Bos taurus*) crossbreed cattle for five microsatellite markers. A linkage map was constructed for the markers and an interval analysis for the presence of QTL was performed. The linkage map indicated differences in the order of two markers relative to the reference map (http://www.marc.usda.gov). Interval analysis detected a QTL controlling birth weight ($p < 0.01$) at 69 centimorgans (cM) from the most centromeric marker with an effect of 0.32 phenotypic standard-error. These results support other studies with crossbred *Bos taurus x Bos indicus* populations.

Key words: BTA5, birth weight, cattle, QTL, microsatellite markers.

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Introduction

The use of crossbred cattle has been an alternative for the intensification of bovine milk production, making possible the exploration of the genetic differences between breeds and the benefits of heterosis. The need for bovine genetic resources adapted to tropical conditions has lead to the use of crosses between Holstein (*Bos taurus*) cattle, selected for milk production for more than 2.000 years (Friend and Bishop, 1978), and Zebu (*Bos indicus*) cattle, adapted to tropical conditions (Madalena *et al.* 1990). Most economically important traits in dairy cattle are quantitative traits, which have been under selection for several generations, with quite favorable results.

The development of saturated genetic maps (Barendse *et al.*, 1997; Kappes *et al.*, 1997; Ihara *et al.*, 2004) has allowed the identification of quantitative trait loci (QTL) affecting economically important traits. MacNeil and Grosz (2002) have stated that the identification of QTL has the potential to significantly increase the genetic improvement rate through the implementation of marker-assisted selection (MAS). For traits difficult or expensive to determine, with low heritability, late expression or measured only after slaughter, MAS can substantially increase the rate of response compared to selection based exclusively on estimates of performance values (Davis and DeNise, 1998). The use of MAS also allows the opportunity for more efficient breakage of antagonistic genetic correlations between characters (Grosz and MacNeil, 2001). For instance, estimates of the genetic correlation between direct effects on birth weight and yearling weight are approximately 0.5 in all bovine breeds (Koots *et al.*, 1994) and as result selection based on mature weight or growth rate to mature weight can significantly increase birth weight potentially increasing the incidence and severity of calving difficulties. The opposite is also true, selection for smaller birth weight will reduce adult weight (Grosz and MacNeil, 2001). Identification of genomic regions affecting birth weight with no ef-

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fect on mature weight would be a powerful tool for the manipulation of pre and post birth growth rate.

Quantitative trait loci have been detected in experimental and commercial bovine, swine and ovine populations (Davis and DeNise, 1998). There are several described bovine QTL affecting many characteristics. Davis *et al.* (1998) detected and mapped five QTL for birth weight on chromosomes 5, 6, 14, 18 and 21 in three families of paternal half-sib Charolais x Brahman (*B. taurus* x *B. indicus*) and Elo *et al.* (1999) detected a QTL for adult live weight on chromosome 23. Stone *et al.* (1999) reported significant evidence for the presence of QTL on chromosomes 1, 2, 5 and 13 and suggestive evidence for QTL on chromosomes 7, 11, 14, 18 and 26 affecting carcass and growth traits in a family of paternal half-sib Brahman cattle. Casas *et al.* (2003) suggested the existence of QTL segregating on chromosomes 5, 6, 7, 13, 14, 17, 19, 22, 27 and 29 for carcass composition and growth in families of Piedmontese and Belgian Blue cattle, both breeds from the *B. taurus* group, while Kim *et al.* (2003) found a total of 35 QTL (five significant and 30 with evidence suggesting linkage) in 19 chromosomes of an experimental F_2 Angus x Brahman population.

Various studies have produced highly significant evidence for the presence of QTL on chromosome 5 affecting different characteristics such as ovulation rate (Kirkpatrick *et al.*, 2000; Arias and Kirkpatrick, 2004), carcass traits (Stone *et al.*, 1999; Casas *et al.*, 2000; Kim *et al.*, 2003) and birth weight (Davis *et al.*, 1998; Casas *et al.*, 2002; Li *et al.*, 2002; Machado *et al.*, 2003b; Kim *et al.*, 2003). The insulin-like growth factor 1 gene (*igf-1*) acting on growth and metabolism maps to chromosome 5. The QTL for growth traits can be attributed to *igf-1* itself or to one or more surrounding genes such as the *high growth* and *myf5* genes, a hypothesis reinforced by the work of Machado *et al.* (2003b) and Kim *et al.* (2003).

QTL fine mapping, which means reducing marker interval near the QTL, is necessary to provide useful reference for future searches for candidate genes which eventually may lead to the identification of the nucleotide substitution(s) underlying the phenotypic variation. This kind of approach usually requires very large and well designed experimental populations appropriate for mapping QTL (Li, 2002) and this is especially true when mapping small effect QTL, although obtaining cattle populations such as these is expensive and time consuming for commercial lines. Even so, since 1995 the Embrapa (*Empresa Brasileira de Pesquisa Agropecuaria*, the Brazilian national agricultural company) Dairy Cattle Research Center has developed a second filial (F_2) generation Gyr x Holstein cattle population using an experimental design with the main aim of creating a population for QTL mapping. The F_2 design is very suitable for mapping economically important loci because not only a considerable amount of phenotypic variability is generated when the first filial (F_1) generation is intercrossed to produce the F_2 generation but linkage disequilibrium between markers and QTL is also promoted. The objective of the work presented in this paper was to use an interval mapping approach to map chromosome 5 for birth weight QTL in the F_2 Gyr x Holstein cattle population.

Materials and Methods

Population

A bovine Gyr x Holstein population of 400 F_2 animals is under development using multiple ovulation with embryo transfer at the Embrapa Dairy Cattle Research Center, Juiz de Fora, Minas Gerais, Brazil. Five F_1 sires and 59 F_1 dams, obtained from crosses between four Holstein sires and 28 Gyr dams, were intercrossed to obtain the F_2 generation. Each F_2 generation animal was weighted within 24 h of birth. For the present study, birth weight data from 294 F_2 animals were available.

Marker selection and genotyping

Marker data were obtained from the MARC-ARS-USDA (Meat Animal Research Center-Agriculture Research Service-United States Department of Agriculture) database at http://www.marc.usda.gov. We chose five microsatellite markers covering the entire chromosome 5 with an average spacing between them of approximately 20 centimorgans (cM), the markers being chosen based on allele number, polymorphism information content, allele range, annealing temperature and primer availability in the Animal Biotechnology laboratory of Embrapa Southeast Cattle (São Carlos-SP, Brazil). An important criterion for locus selection was that the F_1 bulls should be heterozygous for the chosen markers.

All microsatellites were amplified in a final reaction volume of 12.5 μL, consisting of 50 ng of genomic DNA, 50 mM KCl, 1.5 mM $MgCl_2$, 10 mM Tris-HCl pH 8.4, 0.2 μM of each nucleotide, 0.5 units of *Taq* DNA polymerase, and 0.1 μM of each primer. The forward primers for each locus were marked with a fluorescent dye, primer identification codes, annealing temperature, map position and fluorescent dye are summarized in Table 1. Thermocycling conditions consisted of an initial denaturation at 94 °C for 2 min followed by 20 cycles of denaturation at 94 °C for 30 s and primer annealing for 30 s at 10 °C above the annealing temperature of each primer pair which was reduced by 0.5 °C at each cycle (*i.e.* a `touchdown' cycle profile designed to increase the specificity of the PCR reaction). The thermocycles were concluded with 10 cycles of denaturation at 94 °C, primer annealing temperature and primer extension, each for 30 s. Amplification products were submitted to a final extension step at 72 °C for 45 min. Polymerase chain reactions (PCR) were performed in a *Mastercycler Gradient* thermocycler (Eppendorf). At the end of the amplifications, products were analyzed in an *ABI Prism 3100 Avant* sequencer (Applied Biosystems) con-

Table 1 - Primer identification code, annealing temperature, reference map position (http://www.marc.usda.gov) and fluorescent dye used in the experiments.

Primer identification code (markers)	Annealing temperature (°C)	Map position (centimorgans, cM)	Fluorescent dye
BM6026	56	6.7	FAM
BM321	60	38	HEX
BMS1617	54	55.6	NED
BMS490	60	65.4	HEX
BMS1248	58	88.4	FAM

taining four capillaries and which has the capacity to analyze four fluorescent spectra simultaneously. The results were analyzed using the *GeneScan* and *Genotyper* software that calculate the size of the amplified fragments based on the internal size standard GeneScan 500, with fragments between 50 and 500 base pairs.

Statistical analysis

Allelic frequencies and Hardy-Weinberg equilibrium were calculated for the population as a whole and also for each of the generations in the study using the *Cervus 2.0* software (Marshall *et al.*, 1998).

A chromosome 5 linkage map was built using the BUILD and ALL functions of the CRIMAP program (Green *et al.*, 1990) and the parental contribution of each locus was determined using the CHROMPIC function which, starting from the genotypes of a three generation pedigree (parental, F_1 and F_2), allows the determination of the linkage phase of the markers and haplotype identification in the F_2 generation. The map was derived from the observed recombination fraction for each marker interval using Kosambi's mapping function to transform recombination into distance.

This map was used for QTL analysis by the method of multiple interval mapping for F_2 families (Haley *et al.*, 1994) using the *QTL Express* program (Seaton *et al.*, 2002) at http://qtl.cap.ed.ac.uk. The F-statistic was calculated to test the hypothesis of QTL segregation at 1 cM intervals using a model that included the fixed effects of year and season of birth, sex of the calf and additive and dominance effects of the QTL. We also applied permutation tests for the threshold determination (Churchill and Doerge, 1994) and the bootstrap technique for determination of the confidence interval (CI) of the presence of a possible QTL (Visscher *et al.*, 1996). In this study 10.000 permutations were adopted for the value of $\alpha = 0.01$ to obtain stable estimates (Churchill and Doerge, 1994).

The resampling bootstrap method proposed by Visscher *et al.* (1996) to determine the confidence interval removes samples (individuals) of the population that contain information about genotype and phenotype, generating a new population with sample replacement in which statistical analysis is used to identify QTL. After a pre-established resampling number and QTL analysis of the new populations the 95% CI of the QTL is determined by ordering the generated estimates, with 2.5% of the values representing the superior and inferior ends of the distribution. The width of the confidence interval depends on the size of the population and on the QTL effect, although variation between marker spacing does not result in very different confidence intervals (Visscher *et al.*, 1996).

Results and Discussion

Genotypic analysis of parental and F_1 bulls

The purpose of this analysis was to select the most informative markers from the initial panel based on F_1 heterozygosity and chromosome coverage. The microsatellite markers chosen showed polymorphism, covering a segment of about 122 cM, according to the results obtained with the CRIMAP software.

The allelic frequencies of the five markers chosen for the Holstein bulls and Gyr dams are given in Table 2. Seven alleles were identified for markers BM6026 and BMS490, three for BM321, and eight for BMS1617 and BMS1248. It is interesting to observe that many alleles were breed-specific although these data should not be considered representative of the allelic distributions in the Holstein and Gyr populations due to the reduced sample size. They were only estimated with the purpose of verifying the occurrence of allelic divergence among the animals crossed to generate the F_2 progeny.

The heterozygosity of a locus is defined as the probability that an individual is heterozygous for that locus in a population (Liu, 1998). This information is crucial for determining the number of markers needed to expand the linkage map to a desired level of coverage and to determine the number of animals or markers needed to search for economic trait loci (Bishop *et al.*, 1994). As defined by Ott (1992), a locus is considered polymorphic if its heterozygosity (H) is greater than 0.1 and is considered highly polymorphic if H = 0.7. This definition implies that a marker is considered polymorphic when its most frequent allele has a frequency less than 0.95, and highly polymorphic when its most frequent allele has a frequency less than 0.55. Liu (1998) has shown that a sample size as small as 15 specimens can, with reasonable probability, reveal about 70% of the expected heterozygosity of a locus for all the allelic frequency distributions, although a large sample size is needed if the goal is to detect 95% of the heterozygosity.

It is also common to use polymorphism information content (PIC) to quantify marker polymorphism (Botstein *et al.,* 1980), PIC being an estimate of the probability of obtaining informative crosses. Polymorphism information content approximately equals the heterozygosity when the locus has a large number of alleles and, as the number of alleles increases, both PIC and heterozygosity also increase

(Liu, 1998). Our values for PIC, F_1 heterozygosity and probability of Hardy-Weinberg equilibrium are summarized in Table 3.

We found that most of the microsatellite markers in the population studied were highly polymorphic, as expected by the loci pre-selection based on the MARC database, although this was not the case for marker BM321 which presented only three alleles in our research population. Machado *et al.* (2003b) found that in a 5/8 Charolais 3/8 Zebu crossbred population heterozygosity was between 0.468 and 0.755 (average 0.646) for the four markers used in their research. In our study heterozygosity was between 0.578 and 1.0 (average 0.865) (Table 3), this value being higher than the average heterozygosity obtained with nine microsatellites for the Gyr (0.305) and Holstein (0.339) populations by Machado *et al.* (2003a). In a study to incorporate more markers in the bovine genetic linkage map, Bishop *et al.* (1994) found an average heterozygosity of 0.747 in *Bos taurus* X *Bos indicus* F_1 crosses.

Table 2 - Allelic frequencies for parental generation Holstein and Gyr cattle.

Primer identification code (Markers)	Fragment size (bp)	Allelic frequencies (N)	
		Holstein (4)	Gyr (28)
BM6026	148	0.5000	0.1304
	150	0.0000	0.2174
	154	0.1250	0.2391
	160	0.0000	0.0217
	162	0.2500	0.1522
	164	0.1250	0.2174
	166	0.0000	0.0217
	N = 7	1.0	1.0
BM321	104	0.0000	0.1957
	106	0.0000	0.3478
	108	1.0000	0.4565
	N = 3	1.0	1.0
BMS490	170	0.0000	0.3696
	174	0.3750	0.0652
	176	0.0000	0.0652
	178	0.1250	0.0435
	182	0.0000	0.2391
	184	0.5000	0.1739
	194	0.0000	0.0435
	N = 7	1.0	1.0
BMS1617	149	0.3750	0.0000
	151	0.1250	0.0000
	157	0.0000	0.4565
	159	0.1250	0.3043
	161	0.2500	0.000
	163	0.1250	0.0435
	167	0.0000	0.1739
	169	0.0000	0.0217
	N = 8	1.0	1.0
BMS1248	122	0.0000	0.0652
	130	0.0000	0.0217
	132	0.8750	0.0217
	134	0.0000	0.1739
	136	0.0000	0.0870
	138	0.0000	0.3261
	140	0.0000	0.3043
	142	0.1250	0.0000
	N = 8	1.0	1.0

We found that the PIC values of the markers ranged from 0.402 to 0.754, with average of 0.665. According to Botstein *et al.* (1980), a marker can be considered highly informative in a mapping population if it has an expected PIC value greater than 0.5, with values of between 0.5 and 0.25 considered to be reasonably informative. Our data suggest that the parental populations of Gyr and Holstein cattle were sufficiently divergent with respect to the analyzed markers to generate a highly informative F_2 generation.

Of the five markers used to genotype the chromosome 5 only the BM6026 marker showed allelic frequencies for the F_1 generation under Hardy-Weinberg equilibrium (Table 3). The absence of equilibrium was the expected result since the F_1 generation was formed from two different breeds with the purpose of creating new associations between genotype and phenotype in the F_2 generation. The observation of Hardy-Weinberg equilibrium for the BM6026 marker can result from the absence of differences among the allelic frequencies verified for the two breeds, probably due to sample size.

Linkage map construction

The chromosome 5 linkage map constructed by us (Figure 1) showed differences in the marker order of two microsatellites (BMS1617 and BMS490) in relation to the MARC reference map (http://www.marc.usda.gov). According to Liu (1998), this could happen due to the reduced

Table 3 - Polymorphism information content (PIC) values, heterozygosity (H) and probability of Hardy-Weinberg equilibrium (H-W) for the BM6026, BM321, BMS490, BMS1617 and BMS1248 markers in the F_1 generation.

Primer identification code (Markers)	F_1		
	PIC	heterozygosity (H)	Hardy-Weinberg (H-W)
BMS6026	0.753	0.906	NS
BM321	0.402	0.578	$p < 0.01$
BMS490	0.740	0.859	$p < 0.01$
BMS1617	0.754	0.984	$p < 0.01$
BMS1248	0.679	1.0	$p < 0.01$

NS: non-significant ($p > 0.05$). PIC: Polymorphism information content.

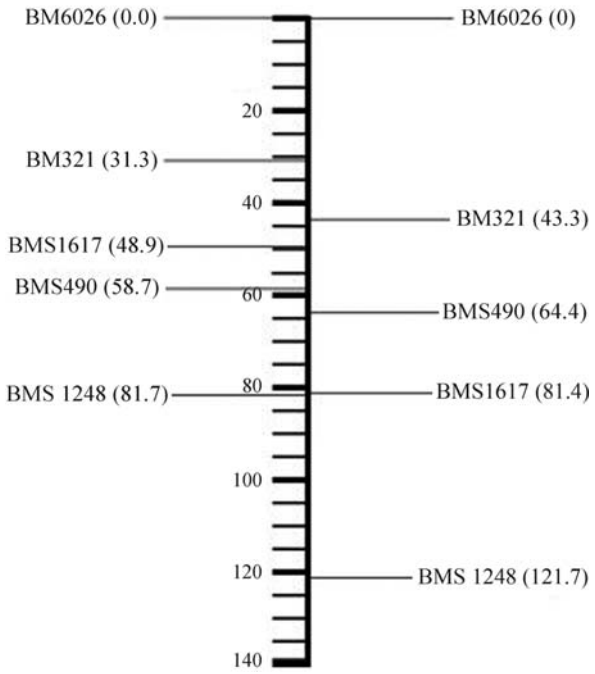

Figure 1 - Linkage map of the markers used in the present study. On the left, the relative positions according to MARC reference map and on the right the Embrapa linkage map obtained in the present work with the F_2 population. The relative positions of the markers on the left were adapted from MARC to consider BM6026 as the most centromeric marker.

sample size used to build the map, because the correct ordering of very close loci implies great number of informative meiosis events. Another hypothesis which could explain the variation in marker order could be the fact that in the MARC reference map two of these markers (BM321 and BMS1248) showed a great number of informative meiosis events while the other markers had a low number of informative meiosis events. The number of informative meiosis events in our map was very homogeneous, except for the BM321 marker for which only three alleles were identified in the population studied. Differences in sample size and the number of informative meiosis events may also explain the fact that the distance (121.7 cM) between the first and the fifth marker in our map was larger than the distance shown in the MARC reference map (81,7 cM). The number of informative meiosis events for the five markers is summarized in Table 4.

QTL mapping

A highly significant QTL ($p < 0.01$) for birth weight was detected in chromosome 5, with an additive effect of -1.6 kg corresponding to approximately 0.32 of the phenotypic standard-error and 5% of the trait average. The highest F-statistics value was at 69 cM from the most centromeric marker between the BMS1617 and BMS490 markers and only 4.6 cM from the BMS490 marker (Figure 2). Bootstrap analysis determined a confidence interval of 40 cM, between 39 and 79 cM, a value considered acceptable for the number of F_2 animals used (Visscher *et al.* 1996). It is important to emphasize that this analysis was performed with 10.000 permutations between genotypes and phenotypes, a much higher value than the value considered by Churchill and Doerge (1994) as being statistically reliable. This QTL effect can be considered as strictly additive, since the estimated dominance deviation (0.735 ± 0.63 kg) was not significant ($p > 0.05$). Machado *et al.* (2003b), in a study with a Canchim population (5/8 Charolais, 3/8 Zebu), detected the presence of a QTL affecting birth weight ($p < 0.05$) located at 82.9 cM from the most centromeric marker and 9.9 cM from the *igf-1* gene towards the telomeric end. However, the identified confidence intervals in Machado *et al.* (2003b) and in the present study do not allow us to conclude that the same QTL is segregating in the two populations. Li *et al.* (2002), using chromosome 5 haplotypes for association studies with growth traits in commercial populations of *Bos taurus* identified three chromosomic regions (0 to 30 cM, 55 to 70 cM, and 70 to 80 cM) that showed significant association with birth

Table 4 - Number of informative meiosis events for each marker on the data used to build the reference map (http://www.marc.usda.gov) and to build the Embrapa map.

Marker	Informative meiosis events	
	MARC	Embrapa
BM6026	201	549
BM321	2081	250
BMS1617	719	420
BMS490	319	536
BMS1248	2699	440

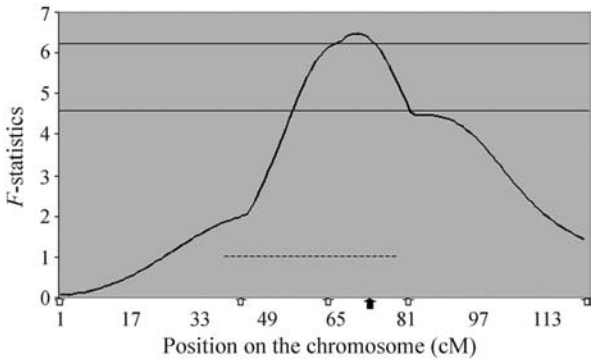

Figure 2 - The F-statistic for body weight (BW) on bovine chromosome 5. The upper and lower horizontal lines represent the threshold levels at 1% (F = 6.44) and at 5% (4.67). The white arrows under the axis indicate the marker positions in chromosome: BM6026 (0.0 cM), BM321 (43.3 cM), BMS490 (64.4 cM), BMS1617 (81.4 cM) and BMS1248 (121.7 cM). The QTL located 69 cM from the centromere (F = 6.49). The black arrow indicates the position of the *igf-1* gene (66.3 cM) adapted from MARC and consider BM6026 the most centromeric marker. The dotted line indicates the confidence interval (39-79 cM) for the QTL.

weight. However, the association of the *igf-1* gene with birth weight was refuted by Machado *et al.* (2003b) and by Li *et al.* (2004), the latter authors having performed candidate gene analysis between the single nucleotide polymorphisms (SNPs) of chromosome 5 and growth and carcass traits. According to Li *et al.* (2004) SNPs detected in the *igf-1* gene should not be responsible, nor even be tightly linked to, the mutation that affects growth and carcass traits in that beef cattle population.

Analysis for the presence of chromosome 5 QTL and their effect on weaning weight (WW) in this F_2 population did not reveal any significant QTL effect (data not shown). This result indicates a tendency towards breaking the high correlation between birth weight and weaning weight, even though a slightly smaller number (N = 290) of animals was used in the weaning weight analysis. This could imply that the selection for this QTL could contribute to minimize the distocia effects since birth weight is the most significant factor that affects the distocia, which in turn affects several traits such as calve and dam mortality, increased susceptibility to disease and smaller calve weaning weight (Grosz and MacNeil, 2001). According to Grosz and MacNeil (2001), the annual losses due to distocia can reach 83.4 million dollars for dairy cattle and 142.5 million dollars for beef cattle in the United States.

The results presented in this paper are consistant with the presence of a QTL for birth weight in bovine chromosome 5 segregating in the F_2 experimental population studied. This QTL has shown to be strictly additive and with no influence on weaning weight, which makes it appropriate for selection in cattle. Further investigation of this chromosome region may allow the identification of favorable haplotypes to be used in marker assisted selection. Analysis of this QTL in the parental Gyr and Holstein populations will also be relevant for the successful incorporation of this information in breeding programs.

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