Research Article

Quantitative trait loci (QTL) mapping for growth traits on bovine chromosome 14

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Abstract

Quantitative trait loci (QTL) mapping in livestock allows the identification of genes that determine the genetic variation affecting traits of economic interest. We analyzed the birth weight and weight at 60 days QTL segregating on bovine chromosome BTA14 in a F2 resource population using genotypes produced from seven microsatellite markers. Phenotypes were derived from 346 F2 progeny produced from crossing *Bos indicus* Gyr x Holstein *Bos taurus* F1 parents. Interval analysis to detect QTL for birth weight revealed the presence of a QTL ($p < 0.05$) at 1 centimorgan (cM) from the centromere with an additive effect of 1.210 ± 0.438 kg. Interval analysis for weight at 60 days revealed the presence of a QTL ($p < 0.05$) at 0 cM from the centromere with an additive effect of 2.122 ± 0.735 kg. The region to which the QTL were assigned is described in the literature as responsible for some growth traits, milk yield, milk composition, fat deposition and has also been related to reproductive traits such as daughter pregnancy rate and ovulation rate. The effects of the QTL described on other traits were not investigated.

Key words: TA14, cattle, F2, growth traits, molecular markers, QTL.

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Introduction

In livestock animals, the main goal of genomic mapping is to identify and characterize genes that affect phenotypic variation in traits of economic relevance. In beef cattle, phenotypic selection for growth has been highly effective due to the ease of measurement and intermediate to high heritabilities (Koots *et al.*, 1994a). There are also moderate to high genetic correlations between growth traits at different ages (Koots *et al.*, 1994b), with selection to increase postnatal growth usually resulting in an increase in birth weight and thus calving difficulty. The increase in postnatal growth maintaining constant birth weight will be facilitated through direct selection based on individual genes or quantitative trait loci (QTL) that influence weight at weaning and at maturity but not during the prenatal period (Kim *et al.*, 2003).

Genetic markers and linkage maps have provided tools to detect QTL in cattle (Stone *et al.*, 1999; Casas *et al.*, 2000; Casas *et al.*, 2001; MacNeil and Gross, 2002) and QTL identification has significantly increased the potential of genetic improvement through implementation of marker assisted selection (MacNeil and Gross, 2002). Most QTL mapping studies have used crosses between *Bos taurus* and *Bos indicus* cattle (Stone *et al.*, 1999; Casas *et al.*, 2000) since the probability of finding segregation on QTL is much higher for crossbred populations (Lynch and Walsh, 1998). As part of a project that will scan the bovine genome for several traits we have produced a reference F2 population from crosses between *B. indicus* Gyr and *B. taurus* Holstein cattle (Gasparin *et al.*, 2005).

Beef cattle QTL for growth traits have been reported in numerous studies (Casas *et al.*, 2000). Davis *et al.* (1998)

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reported significant QTL for birth weight in the centromeric region of bovine chromosome 21 (BTA21) using three half-sib families from *B. taurus* Charolais x Brahman *B. indicus* bulls, in the same position as the most significant QTL for birth weight found by Casas *et al.* (2003). Machado *et al.* (2003) using a composite breed developed from the cross of *B. taurus* and *B. indicus*, detected a QTL for birth weight on the same chromosome. This was probably the same QTL that was segregating in the Gyr-Holstein F2 population described above (Gasparin *et al.*, 2005).

Other authors have identified QTL for growth traits on BTA14, Hetzel *et al.* (1997) having found a region on this chromosome which is significantly associated with the traits birth weight and weights from six to twelve months. Buchanan *et al.* (2000) found a significant marker for weaning weight, yearling weight and average daily gain on pasture at 67 cM and another QTL for birth weight and average daily gain in feedlot mapped to the centromeric region of BTA14.

On the basis of previous studies reporting QTL for growth traits, we investigated the presence of QTL for birth weight and weight at 60 days on BTA14 in an experimental F2 population, obtained from crosses between Gyr and Holstein cattle.

Material and Methods

Animals

An experimental F2 population was produced by the Brazilian agricultural company Empresa Brasileira de Pesquisa Agropecuária (Embrapa) on the Santa Monica Experimental Station, in the Brazilian state of Rio de Janeiro.

The population was started from 28 Gyr females artificially inseminated with semen from four Holstein bulls, resulting in 150 F1 offspring (males and females). Five F1 males were chosen to be the parents of the F2 generation and were crossed with 70 F1 females, preventing kinship between sires and dams, resulting in five families and a total of 346 F2 offspring with birth weight recorded.

DNA extraction

Samples of blood or semen were collected from each animal, including the F1 and F2 parents, for DNA extraction by the method of Hallerman *et al.* (1988).

Markers

Markers were chosen based on map position, number of alleles and heterozygosity, according to information available during February 2004 at the Meat Animal Research Center (MARC) database (http://www.marc.usda. gov). Seven microsatellite markers were selected (CSSM066, ILSTS011, BMC1207, BMS740, BMS1899, BL1036 and BMS2055) that would cover nearly 100% of chromosome 14, at approximately 20 cM intervals based on the United States Department of Agriculture Meat Animal

Research Center (MARC) reference map (http://www. marc.usda.gov).

Genotyping

The polymerase chain reactions (PCR) consisted of 50 ng of genomic DNA, 0.20 mM of dNTPs, 1.5 mM $MgCl_2$, 0.1 µM of each primer and 0.25 units of Taq polymerase (Biotools, Spain) in a total volume of 12.5 µL. For each locus, the forward primer was labeled with either 6-carboxyfluorescein (6-FAM) or 5'-hexachloro-fluorescein phosphoramidite (Hex) fluorochromes. The amplifications were carried out in a *Mastercycler Gradient* thermocycler (Eppendorf), with annealing temperatures specific for each primer. The amplification products were analyzed in an *ABI Prism 3100 Avant* (Applied Biosystems) sequencer with the GeneScan and Genotyper software provided by the manufacturer. Annealing temperatures, fluorescent dyes and the percentage of animals genotyped for each marker in each generation are given in Table 1.

Linkage map

The linkage map of BTA14 was constructed using the build, prepare and all functions of the CRIMAP software (Green *et al.*, 1990). The chrompic function was used to show the grandparental origins of alleles in each offspring's chromosomes, in relation to the linkage phase choice with the highest likelihood. This function gives the relative probability for this phase choice and for the next most likely alternative, displaying the number and location of recombinations on each chromosome, and provides, for each chromosome interval defined by the loci, a list of the chromosomes having a recombination in that interval. The map was derived from the observed recombination fraction for each marker interval using Kosambi's mapping function (Lynch and Walsh, 1998) to transform recombination into distance.

Statistical analysis

To estimate the expected heterozygosity (H_e) and the polymorphism information content (PIC) analysis of the allelic frequencies of the markers was carried out with the Cervus v.2.0 software (Marshall *et al.*, 1998).

The QTL statistical analysis was carried out by the linear regression method (Haley *et al.*, 1994) for F2 pedigrees using the QTL Express software (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. For birth weight and weight at 60 days, the model included the fixed effects of sex of the calf and contemporary group (combination of month and year of birth), calving order of the dam as a covariable and additive effect of the QTL. In this study 1,000 permutations were adopted to obtain stable estimates for the value of $\alpha = 0.01$ (Churchill and Doerge, 1994). Permutation tests were also applied for the threshold determination (Churchill and Doerge, 1994) and the boot-

strap method for determination of the confidence interval (CI) for the presence of a possible QTL (Visscher *et al.*, 1996).

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 can be used to identify QTLs. After a pre-established resampling number and QTL analysis of the new populations the 95% confidence interval (CI) of the QTL is determined by ordering the generated estimates, with 2.5% of the values representing the upper and lower tails 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

Analysis of the seven BTA14 microsatellite markers produced a total of 38 alleles, with an average of 5.24 alleles per locus (Table 1). For any genetic marker, a locus with heterozygosity greater than 70% can be considered as highly polymorphic (Ott, 1999). The number of alleles, heterozygosity and PIC values are show in Table 2. The highest expected heterozygosity was 0.845 for the CSSM066 marker and the lowest was 0.434 for the BMC1207 marker while the average population heterozygosity was 0.716, indicating that most of the markers used in this work were highly polymorphic (Table 1).

The PIC parameter is generally referred to as a measure of usefulness of a marker locus in linkage (Lynch and Walsh, 1998). In our study, the average PIC value in the population was 0.674 and the highest was 0.824 for the CSSM066 whilst the lowest was 0.385 for the BMC1207

marker (Table 1), these being related to the number and frequency distribution of the alleles in both loci.

The chromosome 14 linkage map obtained from our data has the same marker order as the MARC reference map, but the distance between markers was higher. Differences in sample size and in the number of informative meiosis events may also explain the fact that the 144.3 cM distance between the first and the seventh marker in our map (EMBRAPA) was larger than the 104.5 cM distance shown in the MARC reference map. The number of informative meiosis events for the seven markers is summarized in the last two columns of Table 1.

The Haley *et al.* (1994) interval analysis for birth weight on BTA14 resulted in a suggestive QTL (p < 0.05) at 1 cM from the most centromeric marker (Figure 1). The highest F-statistic value (7.62) was at 1.0 cM between the CSSM066 marker at 0.0 cM and the ILSTS011 marker at 16.9 cM. The confidence interval for this QTL was
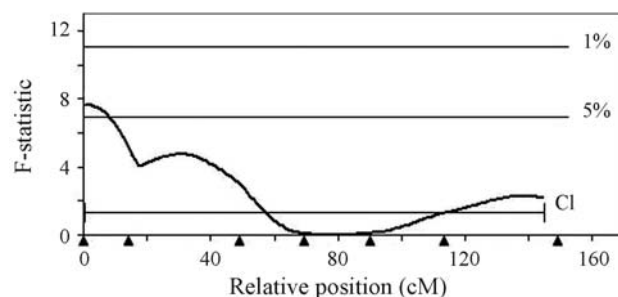

Figure 1 - Chromosome F-statistic distribution for the birth weight quantitative trait locus (QLT) on the chromosome 14 (BTA14). The arrows below the X axis indicate marker positions on the chromosome as measured from the centromere, in centimorgans (cM): CSSSM066 (0.0 cM), ILSTS011 (16.9 cM), BMC1207 (47.8 cM), BMS740 (67.7 cM), BMS1899 (91.6 cM), BL1036 (116.8 cM) and BMS2055 (144.3 cM). The upper and lower horizontal lines represent threshold levels of 1% (F = 11.33) and 5% (F = 7.20). The QTL is located at 1.0 cM from the centromere (F = 7.62). The scale indicates the 95% confidence interval (0.0 cM to 144.0 cM).

Table 1 - Microsatellite markers, annealing temperature (T), fluorescent dye (Dye), number and percentage of F1 and F2 offspring genotyped, number of alleles (A), expected heterozygosity (H_e), polymorphism information content (PIC) and informative meiosis comparing the maps produced by the Brazilian agricultural company *Empresa Brasileira de Pesquisa Agropecuária* (Embrapa) to the reference map produced by the United States Department of Agriculture Meat Animal Research Center (MARC). The markers are placed in order of map position. For each marker we genotyped 32 parent cattle, representing 100% of parents.

	Reaction conditions		Genotyped offspring (%)		Allele data			Embrapa		MARC	
Marker	T (°C)	Dye*	F1	F2	A	H_e	PIC	Informative meiosis	Map position (cM)	Informative meiosis	Map position** (cM)
CSSM066	60	HEX	72 (98)	369 (99)	7	0.845	0.824	574	0.0	241	0
ILSTS011	58	6-FAM	71 (96)	361 (97)	3	0.665	0.590	641	16.9	265	5.6
BMC1207	58	HEX	72 (98)	337 (91)	4	0.434	0.385	324	47.8	839	31.2
BMS740	58	HEX	72 (98)	361 (97)	6	0.826	0.800	626	67.7	422	39.2
BMS1899	58	6-FAM	72 (98)	364 (98)	6	0.781	0.747	623	91.6	363	47.0
BL1036	56	6-FAM	72 (98)	368 (99)	8	0.784	0.757	548	116.8	249	73.7
BMS2055	58	HEX	72 (98)	360 (97)	4	0.674	0.617	459	144.3	422	79.1

*HEX = 5'-hexachloro-fluorescein phosphoramidite, 6-FAM = 6-carboxyfluorescein.
**Setting CSSM066 as the most centromeric marker.

144.0 cM, from 0.0 to 144.0 cM in relation to CSSM066, the most centromeric marker. The sex effect was estimated to be -1.926 ± 0.570 kg for the females due to the difference of size between males and females and the additive effect was of 1.210 ± 0.438 kg, corresponding to 4% of the trait mean of 29.59 kg. The QTL allele with a positive effect on birth weight was inherited from the Holstein parental breed.

For weight at 60 days the interval analysis on BTA14 resulted in a suggestive QTL (p < 0.05) at 0 cM from the most centromeric marker (Figure 2). The highest F-statistic value (8.34) was at 0.0 cM, close to the CSSM066 marker at 0.0 cM. The confidence interval for this QTL was 137.5 cM, from 0.0 to 137.5 cM in relation to the most centromeric marker (CSSM066). The sex effect was estimated to be -4.178 ± 0.994 kg for the females and the additive effect was 2.122 ± 0.735 kg, corresponding to 7.2% of the trait mean of 29.59 kg. The QTL allele with positive effect on birth weight was inherited from the Holstein parental breed.

Discussion

In this study we constructed a linkage map based on genotype data using a three generation pedigree in a F2 genetic design. Although markers were selected to cover the whole BTA14 at a spacing of 20 cM, the map built from the observed informative meiosis resulted in an average interval between markers of 23.36 cM. The inclusion of additional markers in these intervals would increase the probability of detecting a QTL and could also increase the significance level of the QTL for birth weight and weight at 60 days described in this paper. The position of the QTL found in this study coincides with the centromeric region of the QTL found by Morris *et al.* (2002), who found a BTA14 QTL between about 10 to 30 cM which influenced growth traits such as weight at 250 and 600 days, weight gain from

Figure 2 - Chromosome F-statistic distribution for the weight at 60 days quantitative trait locus (QLT) on the chromosome 14 (BTA14). The arrows below the X axis indicate marker positions on the chromosome as measured from the centromere, in centimorgans (cM): CSSM066 (0.0 cM), ILSTS011 (16.9 cM), BMC1207 (47.8 cM), BMS740 (67.7 cM), BMS1899 (91.6 cM), BL1036 (116.8 cM) and BMS2055 (144.3 cM). The upper and lower horizontal lines represent threshold levels of 1% (F = 9.61) and 5% (F = 6.98). The QTL is located at 0.0 cM from the centromere (F = 8.34). The scale indicates the 95% confidence interval (0.0 cM to 137.5 cM).

the 250 to the 400 days, gain of weight from the 400 to the 600 days and also hot carcass weight.

Other studies relating the BTA14 chromosome to growth traits have been described in the literature. Kneeland *et al.* (2004) identified haplotypes on BTA14 associated with three growth traits in a commercial *Bos taurus* line, with some of the haplotypes involving three of the markers (CSSM066, BMC1207 and BMS1899) used in the study described in the present paper. Kneeland *et al.* (2004) showed that haplotypes involving the BMC1207 marker at 36.2-46.2 cM and the BMS1899 marker at 52.0-67.7 cM were associated with birth weight while the haplotypes involving the CSSM066 marker at 17.0-24.0 cM and the BMC1207 marker at 36.2-46.2 cM were associated to postweaning average daily gain (ADG) on feed. Mizoshita *et al.* (2004) found five QTL related to growth traits on BTA14. ADG from 9 to 30 months during fattening, body weight at slaughter and carcass weight were located at the 45-51 cM region, while body weight at 9 months before fattening and ADG before fattening were located at the 29-42 cM region.

The centromeric end of BTA14 corresponds to the telomeric end of human chromosome 8, an homology supported by a combination of cross-species chromosome painting analysis (Zoo-FISH) (Solinas-Toldo *et al.* 1995), comparative anchor tagged sequences (CATS) (Lyons *et al.* 1996) and linkage mapping using thyroglobulin restriction fragment length polymorphisms (RFLPs) (Barendse *et al.* 1994). Refining the map position of the identified QTL with linkage disequilibrium mapping should allow more precise boundary identification of the orthologous human chromosome segment, providing a list of positional candidate genes and expressed sequence tags (ESTs) (Coppieters *et al.* 1998).

With the availability of the draft sequence of the bovine genome the search for clones of the bovine genome on bacterial artificial chromosomes (BACs) containing the QTL flanking markers would be a straight forward strategy for candidate gene discovery and gene expression analysis. In the absence of a complete and annotated bovine genome sequence, detailed human-bovine comparative maps are one of the most effective tools for identification of positional candidate genes contributing to cattle QTL (Connor *et al.*, 2006).

We found that in the F2 population (Gyr X Holstein) analyzed by us the centromeric region of the chromosome 14 influences growth traits. This not only support previously published results in the literature but also creates opportunities for other studies on candidate genes, single nucleotide polymorphism (SNP) and gene expression. Birth weight and weight at 60 days could be considered as a reproductive trait rather than a growth trait, since delivering heavier calves may affect the reproductive performance of a dam. Ashwell *et al.* (2004) found a daughter pregnancy rate (DPR) QTL between the CSSM066 and ILSTS011
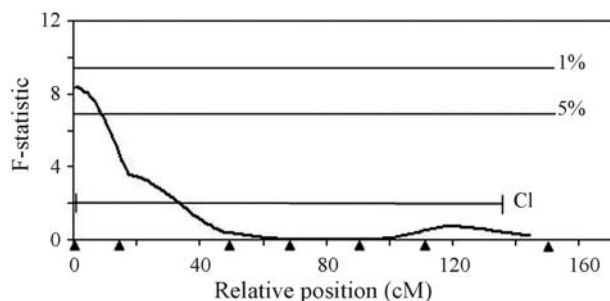
markers at 11 cM, while Schnabel *et al.* (2005) have placed a DPR QTL between the BMC1207 and BMS1899 markers with a significance level of $p < 0.05$. The effects of DPR QTL may be explained by the nearby *DGAT1* gene (Ashwell *el al*. 2004). Gonda *et al.* (2004) identified a QTL affecting ovulation rate on BTA14 in the USDA MARC twinning herd at 59 cM, potentially representing the same DPR QTL gene.

Exploring the QTL information on Gyr and Holstein breeding programs would require the confirmation of QTL segregation within each population as well as the effect on other traits.

Acknowledgments

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