IDENTICAL BY DESCENT HAPLOTYPE SHARING ANALYSIS : APPLICATION IN FINE MAPPING OF QTLS FOR BIRTH WEIGHT IN COMMERCIAL LINES OF *BOS TAURUS*

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INTRODUCTION

Identification and mapping of quantitative trait loci (QTL) for birth weight in beef cattle have been reported (Davis *et al.,* 1998 ; Stone *et al.,* 1999). Fine mapping of these QTLs will greatly facilitate the identification and cloning of the causative genes. It is expected that individuals within a semi-closed population, such as a commercial line of cattle, may be derived from one or a limited number of founders. Thus, some common haplotypes originating from the common ancestors should carry on and segregate among the individuals of the breeding line, particularly when selection is applied. These common haplotypes may harbor QTLs of interest and make it possible to locate QTLs segregating in the line. We discuss here the application of the identical by descent (IBD) haplotype sharing analysis in fine mapping of QTLs for birth weight in commercial lines of *Bos taurus*.

MATERIALS AND METHODS

Animals and phenotypic data. Animals from two commercial lines of Beefbooster Inc., Canada were used. The M1 line was developed from an Angus base and the M3 line was developed from small cows of various breeds. Both lines have been under selection for 30 years and the selection criteria for the lines are based on indices described by MacNeil and Newman (1994). The DNA samples and birth weight EBV data (estimated breeding value) of the animals were provided by Beefbooster.

Genotyping and haplotype identification. One hundred seventy six male calves and their 12 respective sires (9-30 calves of each sire) of the M1 line were genotyped using 16 microsatellite markers from BTA5. In order to verify the results from the M1 line, an additional 170 male calves and their 14 respective sires of the M3 line were genotyped using 9 markers chosen from BTA5. Alleles of each locus contributed by the sire as well as by the dam were identified for each calf by examining the genotype of their sires. The haplotypes of each male calf were then established along the chromosome.

Statistical analysis. Regression analyses were performed between the most commonly observed haplotypes and the birth weight EBV data using a general linear model (GLM) procedure, in which the difference between animals with the haplotype and animals without the haplotype or with uncertain haplotypes was tested. The comparison-wise and chromosome-

wise thresholds of the p value were generated empirically from the permutation method outlined by Churchill and Doerge (1994). A type I error of 0.05 and 0.10 was used for calculating comparison-wise and chromosome-wise p-value thresholds, respectively. In comparison, an interval QTL mapping method developed by Seaton *et al.* (2001) was also used for QTL analysis.

RESULTS AND DISCUSSION

Two haplotypes were found having association with the birth weight EBV above the comparison-wise p-value threshold in the M1 line and five in the M3 line (table 1). On average, the haplotypes have an effect of 0.62 standard deviations (S.D.) on the birth weight EBV, ranging from 0.36 S.D. to 0.84 S.D. All the haplotypes have negative effects on the birth weight EBV except for haplotype *BMS490-6, IGF1-1* in the M3 line, which has a positive effect on the birth weight EBV (table 1). Figure 1 depicts the common haplotypes with the lowest p-values for the birth weight EBV association along BTA5 for the M1 line (1a) and the M3 line (1b).

Table 1. Association between haplotype and birth weight (EBV) in the M1 and the M3 lines of *Bos taurus* from Beefbooster Inc

Line/Haplotype [A]	P-value[B]	Haplotye effect [C]
M1		
BP1-4, BL23-3	0.0042**	-0.78 S.D
BMS490-2, ETH10-4	0.0561*	-0.54 S.D
M3		
BP1-2, BL23-4	0.0229*	-0.75 S.D
BMS490-4, IGF1-2	0.0636*	-0.36 S.D
BMS490-6, IGF1-1	0.0318*	+0.84 S.D
BMS490-6, IGF1-2	0.0091*	-0.48 S.D
IGF1-2, BM1819-3	0.0260*	-0.58 S.D

[A] The haplotypes were named by two alleles of a pair of loci. For example, haplotype *BP1-4*, *BL23-3* represents a segment of chromosome having allele 4 of *BP1* and allele 3 of *BL23*.

[B] "*" and "**" indicate the p-values above the comparison-wise threshold and chromosome-wise threshold, respectively.

[C] S.D. = standard deviation, "+" and "-" represent positive and negative effects, respectively.

In the M1 line, haplotype *BP1-4, BL23-3* and *BMS490-2, ETH10-4* have significant associations with the birth weight EBV above the chromosome-wise and the comparison-wise threshold, and are located in the chromosomal regions of 20 cM to 30 cM and 65 cM to 70 cM, respectively. In the M3 line, five haplotypes are significantly associated with the birth weight EBV above the chromosome-wise threshold. Haplotype *BP1-2, BL23-4* lies in the same chromosomal region to that of haplotype *BP1-4, BL23-3* in the M1 line. In the chromosomal region of 65 cM to 78 cM, haplotype *BMS490-4*, *IGF1-2 ; BMS490-6, IGF1-1 ; BMS490-6, IGF1-2* and *IGF1-2, BM1819-3* have significant associations with the birth weight EBV. Even though more haplotypes were identified having significant effects on the birth weight EBV in

the M3 line than in the M1 line and the phases of the haplotypes associated with the birth weight EBV in both lines are different, the two chromosomal regions in which the haplotypes lie are the same. In another study, we also identified two chromosomal regions on BTA5 that have significant associations with the actual birth weight (Li *et al.,* 2001). It was found that the two chromosomal regions identified were the same between the two studies.

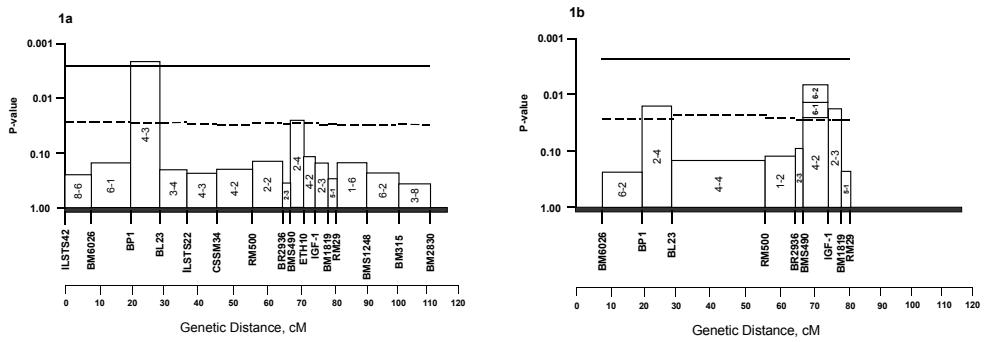

Figure 1. Haplotypes with the lowest p-values between two adjacent loci along BTA5 for the birth weight EBV for the M1 line (1a) and the M3 line (1b) of *Bos taurus* from Beefbooster Inc. using the IBD haplotype sharing analysis. The dash line ---- and solid line — represent the comparison-wise and the chromosome-wise p-value threshold levels, respectively.

QTLs for birth weight have been mapped in bovine chromosome 5 in the region of 70 to 110 cM by Davis *et al.* (1998), and in the region of 50 to 85 cM by Stone *et al.* (1999). In this study, we identified a similar chromosomal region of 65 to 75 cM associated with the birth weight EBV in the M1 line as well as in the M3 line. We have also identified an additional chromosomal region of 20 cM to 30 cM that has a significant effect on birth weight. Whether there are one or more new QTLs in this region is unclear at present.

The interval QTL mapping analysis detected QTLs in similar, but wider, chromosomal regions in both lines to those identified in the IBD haplotype sharing analysis (figure 2). In the M1 line, the chromosomal regions of 0 cM to 38 cM and 70 cM to 110 cM were above the LOD of 2.0 in the interval mapping analysis. There are several peaks within each region, however. In the first region, the peak of 20 cM was in the same location as that in the IBD haplotype sharing analysis, even though it was not the highest peak. In the second region, the highest peak of 75 cM lay in the same location as that in the IBD haplotype sharing analysis. In the M3 line, the interval mapping approach identified the two chromosomal regions of 25 cM to 50 cM and 60 cM to 80 cM at the LOD of 2.0. Each chromosomal region covered more than 20 cM in distance, even though they were located in the same areas as in figure 1 (1b). Obviously, the QTL regions detected using the interval mapping approach were less defined than those detected using the IBD haplotype sharing analysis. That may be due to the small sample size of each family (less than 30), which is very common in commercial lines of *Bos taurus*. The IBD

haplotype sharing analysis takes advantage of linkage disequilibrium in populations with limited outbreeding, in which common chromosome segments are shared by individuals in populations that originated from a few common founders. The chromosome segments that house the QTL can be identified through direct haplotype comparison. This method exploits the historical recombinations rather than generating new ones. Moreover, the IBD haplotype sharing analysis can easily single out individuals with haplotypes of interest and make them useful reference groups for further candidate gene study.

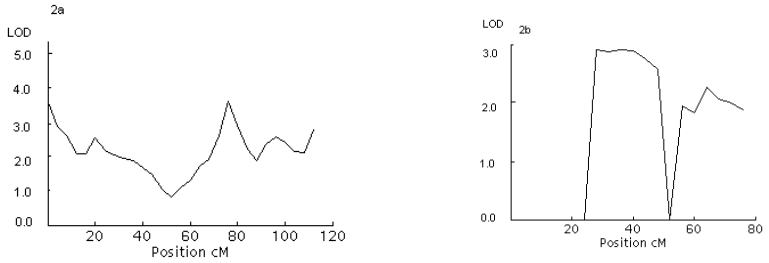

Figure 2. QTL analysis profile for BTA5 for the birth weight EBV using the interval mapping method for the M1 line (2a) and the M3 line (2b) of *Bos taurus* from Beefbooster Inc

CONCLUSION

The IBD haplotype sharing analysis has shown its feasibility in fine mapping QTLs in commercial lines of beef cattle. The study should provide a useful reference for QTL mapping in commercial lines of beef cattle as well as of other livestock species.

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