MAPPING QTL FOR MILK PRODUCTION TRAITS IN NORWEGIAN CATTLE

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SUMMARY

The search for QTL affecting milk production traits is undertaken in Norwegian Cattle using a granddaughter design. Six grandsires with an average of 48 sons each were genotyped for close to 300 DNA markers evenly distributed and covering around 2700cM of the cattle genome. Two and three-point linkage analyses are developed to construct a male genetic map of Norwegian Cattle. Preliminary result of a QTL located on chromosome 6 and affecting milk yield is reported.
Keywords: genetic map, interval mapping, QTL, bovine

INTRODUCTION

Mapping Quantitative Trait Loci (QTL) is the search for the loci responsible for production traits aided with genetic markers. A whole genome scan for QTL detection has been undertaken using available records of performance from national evaluation and close to 300 DNA markers. The average distance between adjacent markers was 9.5 cM .

Approximate power for a granddaughter design with a type 1 error of .01 using the breeding structure of Norwegian Cattle (6 sires and 50 sons per sire with 250 daughters each) is shown in Table 1. The power was computed following Weller *et al.* (1990). It can be observed that the potential for QTL detection in our data structure ranges from .2 to .4 phenotypic standard deviations.

The objectives of this paper are to present methods and preliminary results on QTL mapping of chromosome 6 for milk production traits in Norwegian Cattle.

Table 1. Power of a granddaughter design in Norwegian Cattle with a type 1 error of .01. The frequency of heterozygous sires is assumed to be .5. Heritabilities (h^2) of .10, .20, and .40 are considered.

	Gene effect in residual phenotypic standard deviations				
	.10	.20	.30	.40	.50
$h^2 = .10$	.12	.66	.92	.97	.98
$h^2 = .20$	.05	.36	.76	.92	.96
$h^2 = .40$	.03	.15	.44	.73	.88

Construction of a male genetic map of markers

For the construction of the linkage map we look upon the meioses observed in sires through the gametes inherited to their half-sib sons. In some cases, the allele inherited from the sire can not be traced to the sons since sire and sons may have the same genotype at the marker. If those sons are not used then an ascertainment bias may occur. Two and three-point linkage analyses using all sire families and sons were developed (Gomez-Raya, 1997). The software uses the grid search method to find the maximum likelihood estimate of recombination rate using all sires and linkage phases. Analyses for each individual sire family were performed to reconstruct the linkage phase for each chromosome and sire. It was accomplished by computing the probability of each phase conditional on the observations for each pair of adjacent markers. The markers utilised in our QTL project were taken from different published cattle genetic maps (Barendse *et al.*, 1994; Bishop *et al.*, 1994; Kappes *et al.*, 1997). Order of loci was decided based on both published results and the best supported order obtained after the three-point linkage analyses. Maximum likelihood method can efficiently give the right order of the loci when three or more sire families of large size are used. However, for small number of sire families the method is not very efficient.

Interval mapping for QTL detection

The records of performance corresponding to disease resistance, milk production and fertility traits are currently being edited. However, estimated breeding values for milk, fat, and protein yields of sons from national evaluation were available and were used to obtain preliminary results. The first step was to re-generate right hand side to Mixed Model Equations (MME) with fixed effect of national evaluation absorbed out according to Lien *et al.* (1995). The second step was to compute all recombination fractions as described above and to reconstruct the linkage phase of the chromosomes for each sire. The third step was to carry out interval mapping according to the mean model:

$$y_{ijk.} = s_i + m_{ij} + a_{ijk} + e_{ijk.},$$

where, $y_{ijk.}$ = re-generated right hand side to Mixed Model Equations (MME) with fixed effect of national evaluation absorbed out for the k^{th} son with j^{th} QTL genotype inherited from the i^{th} bull sire, s_i = fixed effect of i^{th} bull sire (i = 1 to 6), m_{ij} = fixed effect of j^{th} QTL genotype (j = 1 to 2) nested within the i^{th} bull sire, a_{ijk} = random effect of k^{th} son nested within the j^{th} QTL genotype of the i^{th} bull sire, and $e_{ijk.}$ = random residual effect.

The construction of the incidence matrix corresponding to fixed effects was modified to make use of flanking markers information in the following way. Elements corresponding to each son inheriting QTL alleles from his sire is replaced by the conditional probabilities of inheriting either allele when assuming Haldane's rule. The model is evaluated within each interval of two markers and every 1 cM. The F-value was computed to test over all sire families. This method is similar to the within-sire regression proposed by Knott *et al.* (1994) but incorporates a random effect of son, which can account for the residual component of the breeding value. Permutation tests (Churchill and Doerge, 1994) with 10000 shuffles were carried out to account for multiple testing in chromosome 6. Only comparisonwise and chromosomewise threshold values were computed. A permutation test when the model includes a random effect is very demanding computationally due to the large number number of equations to be

Table 2. Probability of the most likely linkage phase given the observations for chromosome 6 in the analysis of individual families and genetic distances (in cM) using Kosambi map function.

Sire	ILSTS93	ILSTS90	BM1329	BM143	BM4528	RM28	BP7	BMC4203	BM2320
2005		X	~1	~1		~1	~1		.94
2052	X	~1	.85	~1		.74			.59
2402	X		.94	~1	~1	~1	~1	.94	~1
2463	X	~1	1	~1	~1	~1	.99		.98
2946	X		.94	~1	~1	~1		.50	~1
3131	X		~1	~1	~1		.91	~1	~1
Distance	X	5.4	22.1	15.7	14.6	7.2	19.5	28.5	15.5

solved. The computing strategy we developed was 1) create left and right hand side of the MME, 2) solve for the real data 3) store the g-inverse of the left hand side of the MME, 4) create a permutation of observations and construct the right hand side of MME, 5) solve MME, and 6) repeat 4 and 5 until the total number of shuffles is completed.

RESULTS AND DISCUSSION

Table 2 illustrates the marker information for chromosome 6 available. In this table 'X' is the first informative marker in that family, and the number under the next marker is the conditional probability of the most probable linkage phase given the observations. For example, for sire 2052 the probability between ILSTS93 and ILSTS90 is ~1 and between ILSTS90 and BM1329 is .85. Among the assumptions for interval mapping is that the linkage phase between markers is known. It can be observed that it is the general case with the exception of two families in a chromosomal region. Map distances agreed well with other published maps (e.g. Kappes *et al.*, 1997).

The results for interval mapping for chromosome 6 are presented in Figure 1. A peak with F-value of 3.67 for milk yield between markers BM143 and BM1329 was observed. The chromosomewise threshold at 1% is 3.50. We are currently developing methods to account for multiple testing in the entire genome. Note that the peak was observed in the chromosomal region with more information (Table 2). The estimates of the QTL effect for milk yield ranges between .30 and .45 phenotypic standard deviations in the three families with higher contrasts values, which is the range of the power for our population structure (Table 1). This result is also consistent with other findings of a QTL in chromosome 6 affecting milk yield but with no influence on protein yield (Georges *et al.*,1995; Kühn *et al.*,1996). The segregation of QTL for milk yield of relatively large size in highly selected populations for milk production could be due to epistatic interactions between the alleles at the QTL and alleles at other loci which is not accounted for in the methods used for QTL detection.

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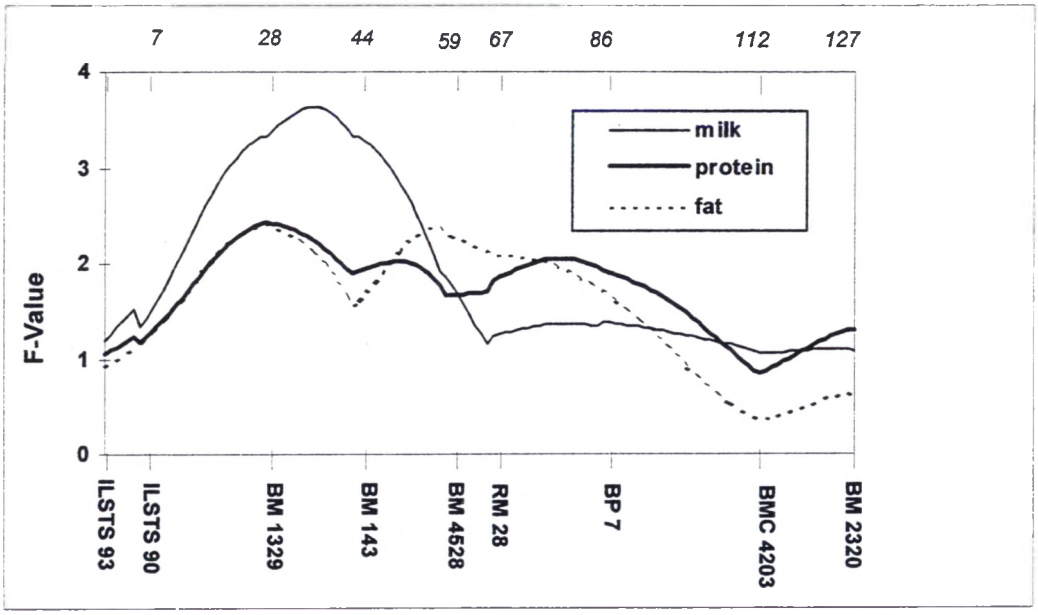

Figure 1. F-value of interval mapping for milk, protein, and fat yields for chromosome 6. Abscissa in the top represents the map distances. Abscissa in the bottom are the microsatellite markers

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