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Quantitative trait loci affecting clinical mastitis and somatic cell count in dairy cattle

Helge Klungland,[1] Ayman Sabry,[1] Bjørg Heringstad,[1] Hanne Gro Olsen,[1] Luis Gomez-Raya,[1,*] Dag Inge Våge,[1] Ingrid Olsaker,[2] Jørgen Ødegård,[1] Gunnar Klemetsdal,[1] Nina Schulman,[3] Johanna Vilkki,[3] John Ruane,[1,] Monica Aasland,[1] Knut Rønningen,[2] Sigbjørn Lien[1]**

[1]Department of Animal Science, Agricultural University of Norway, P.O. Box 5025, N-1432 Ås, Norway
[2]Department of Morphology, Genetics and Aquatic Biology, Norwegian College of Veterinary Medicine, P.O. Box 8146 Dep., N-0033 Oslo, Norway
[3]Agricultural Research Centre MTT, Animal Production Research, Animal Breeding, FIN-31600 Jokioinen, Finland

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Abstract. Norway has a field recording system for dairy cattle that includes recording of all veterinary treatments on an individual animal basis from 1978 onwards. Application of these data in a genome search for quantitative trait loci (QTL) verified genome-wise significant QTL affecting clinical mastitis on Chromosome (Chr) 6. Additional putative QTL for clinical mastitis were localized to Chrs. 3, 4, 14, and 27. The comprehensive field recording system includes information on somatic cell count as well. This trait is often used in selection against mastitis when direct information on clinical mastitis is not available. The absence of common QTL positions for the two traits in our study indicates that the use of somatic cell count data in QTL studies aimed for reducing the incidence of mastitis should be carefully evaluated.

Introduction

Mastitis is the most frequent and costly disease in dairy production. In Norwegian cattle (NRF), several functional traits have been included in the breeding goal, including disease resistance and fertility traits (Heringstad et al. 2001; Karlsen et al. 2000; Lien et al. 2000). Norway was the first country to establish a nationwide health recording system for dairy cattle, and it and Denmark, Sweden, and Finland are the only countries with a health recording system (Heringstad et al. 2000). Therefore, exceptional data for genetic studies on disease resistance, among them clinical mastitis, are available for NRF.

Clinical mastitis is inherited with an unfavorable genetic correlation to milk production, and has to be included in the breeding program in addition to milk production for avoiding an increased frequency of mastitis (Heringstad et al. 1999; 2001). Clinical mastitis has been included in the Norwegian breeding program since 1978 (Solbu 1983). Since information on clinical mastitis is not generally available, several breeding programs use indirect selection based on somatic cell count (SCC). Distinct from clinical mastitis, the basic SCC level does not depend upon any inflammation. Consequently, there is no direct connection between low SCC levels and the probability for getting mastitis. In Norwegian dairy herds, both mastitis and SCC are recorded. With these unique data, this breed is a resource for comparing these two traits in QTL studies, as well as in other genetic studies.

Correspondence to: H. Klungland, E-mail: helge.klungland@ihf.nlh.no

**Present address:* Centre UdL-IRTA, Area de Produccio Animal, Av. Alcalde Rovira Roure, 177, 25198 Lleida, Spain.

***Present address:* FAO, Animal Production and Health Division, Viale delle Terme di Caracalla, 00100 Rome, Italy.

Table 1. Families of the Norwegian cattle breed used in the QTL study. Number of sons and number of granddaughters with clinical mastitis and SCC records per sire family are given. All sons were progeny tested based on at least 200 daughters (average number of daughters are in brackets).

	Sons	Granddaughters	Sons	Granddaughters
Bull sire	Clinical mastitis		SCC	
2005 Smidesang	71	62,534 (881)	71	65,437 (922)
2052 Mauland	32	40,302 (1259)	32	42,052 (1314)
2402 Thorset	54	51,058 (946)	54	48,789 (904)
2463 Jørgentvedt	39	45,439 (1165)	39	43,837 (1124)
2946 Bekkevold	42	17,597 (419)	42	15,772 (376)
3131 Okkelberg	47	19,957 (425)	46	13,220 (287)
Total	285	236,887 (831)	284	232,107 (817)

In Norway, the heritability of SCC has been estimated at 0.11 (Ødegård et al. 2001), and the genetic correlation between SCC and clinical mastitis has been reported to range from 0.30 to 0.97 (Emanuelson et al. 1988; Lund et al. 1999; Pösö and Mäntysaari 1996; Rupp and Boichard 1999; Shook and Schutz 1994; Weller et al. 1992). Although some of these findings indicate a relatively strong genetic correlation between SCC and mastitis, the low genetic correlation in first lactation reported by Pösö and Mäntysaari (1996) indicates that clinical mastitis and SCC monitor different characteristics of udder health. Therefore, a comparison of QTL affecting clinical mastitis versus SCC should be of great interest. Furthermore, QTL affecting mastitis in NRF have the potential of being used also in populations lacking this information, through marker-assisted selection.

On the basis of the design studies by Gomez-Raya et al. (1998), it was shown that the power of detecting a QTL of a given effect is higher for low heritable traits than for those with high heritability, amounting to 0.92 for a trait with heritability of 0.10 and a QTL-effect of 0.3 phenotypic standard deviation. The main objective of this study was to use the unique data for clinical mastitis and SCC in the NRF population in a whole-genome search for QTL.

Materials and methods

Animals. All animals were NRF, which is a heterogeneous population of cattle based on local breeds and Ayrshire, Swedish Red-and-White, Friesian/Holstein (Felius 1995). Animals from six half-sib families with a total of 285 sons were used in the study (Table 1).

Marker map. The Norwegian Cattle Map (NCM), available at http://www.nlh.no/Institutt/IHF/Genkartstorfe/, was utilized in the study (Våge et

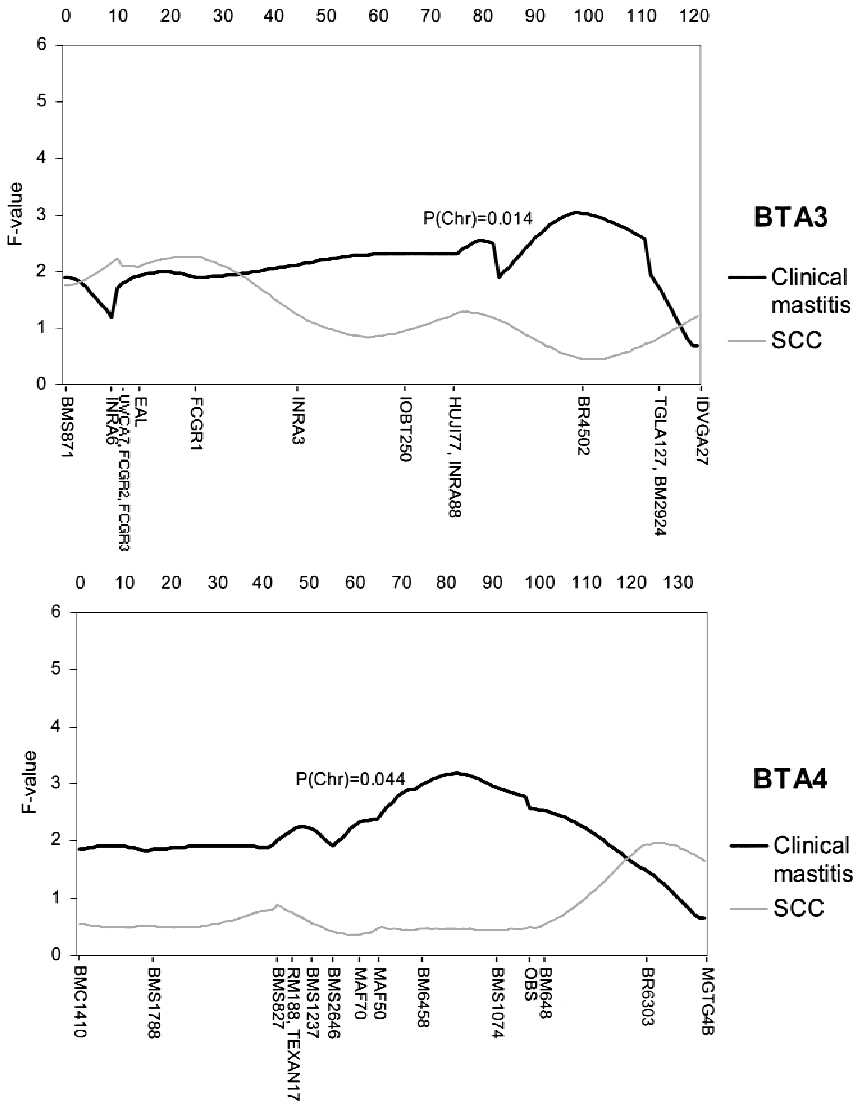

Fig. 1. Across-family QTL results for clinical mastitis in Norwegian cattle were localized to bovine Chrs 3, 4, 6, 14, and 27. Results obtained for somatic cell count (SCC) are also included. Genome-wise (BTA6) and chromosome-wise significance levels for clinical mastitis are noted, while results for SCC were not significant for any chromosomes.

al. 2000). This male genetic linkage map was constructed by using the six half-sib families (Table 1) and covers all 29 autosomes. The NCM summarizes to a total length of 2682 cM, with an average interval of 12.5 cM from 288 analyzed markers, of which 261 were anonymous microsatellites and 27 were coding genes. To achieve higher marker density in specific chromosome regions (see Fig. 1, 2), 12 additional markers were genotyped using primers and PCR conditions described at USMARC Genome Database (http://sol.marc.usda.gov/; Kappes et al. 1997). These markers were positioned by using the CRIMAP package (Green et al. 1990) and the Haldane map function.

Performance data. Clinical mastitis records of 236,887 first lactation NRF cows, which is a subset of the data presented in Heringstad et al. (1999, 2001), were used in the study (Table 1). Clinical mastitis was defined as a binary trait, based on whether or not the cow had at least one veterinary treatment of clinical mastitis in the period from 15 days before to 120 days after first calving. The mean frequency of clinical mastitis in the data was 17%. Corresponding records of lactational means of somatic cell count (LSCC) for 232,107 first lactating cows (Table 1) were extracted from the data set analyzed by Ødegård et al. (2001). Clinical mastitis and LSCC records for each cow were pre-corrected for fixed effects of age at calving, month of calving, and herd x year, according to results of Heringstad et al. (2001) and Ødegård et al. (2001), respectively. Daughter yield deviation (DYD) for each cow was defined as response (clinical mastitis of LSCC) corrected for all fixed effects in the model, and mean DYD for each sire was calculated and used in a granddaughter design (Weller et al. 1990).

Interval mapping. Statistical analysis for both traits followed the multiple marker regression method of Vilkki et al. (1997), according to the following model:

$$y_{ijk.} = \mu + a_i + b_i X_{ijk} + e_{ijk} \quad (1)$$

where $y_{ijk.}$ = mean daughter yield deviation for clinical mastitis or LSCC of bull k, inheriting marker allele j from sire i, μ = overall mean, a_i = effect of the ith bull sire (i = 1 to 6), b_i = regression coefficient within bull sire i, x_{ijk} = probability of the QTL allele being transmitted from bull sire i, given the pair of flanking markers j of bull k, $e_{ijk.}$ = residual effect Chromosome-wise significance threshold values were determined empirically by using 10,000 permutations at each cM (Churchill and Doerge 1994). Genome-wise significance levels, taking into account testing of the whole genome, were calculated as: $P_{genome} = 1-(1-P_{chromosome})^{1/r}$, where (r) was obtained by dividing the length of a specific chromosome by the total length of the autosomal genome (de Koning et al. 1999). Confidence interval was calculated by bootstrapping according to Visscher et al. (1996).

Results

With an average of more than 130 informative offspring per marker, and 300 markers, close to 40,000 genotypes were analyzed. In total, five suggestive QTL affecting clinical mastitis were detected that were chromosome-wise significant (Chrs 3, 4, 6, 14

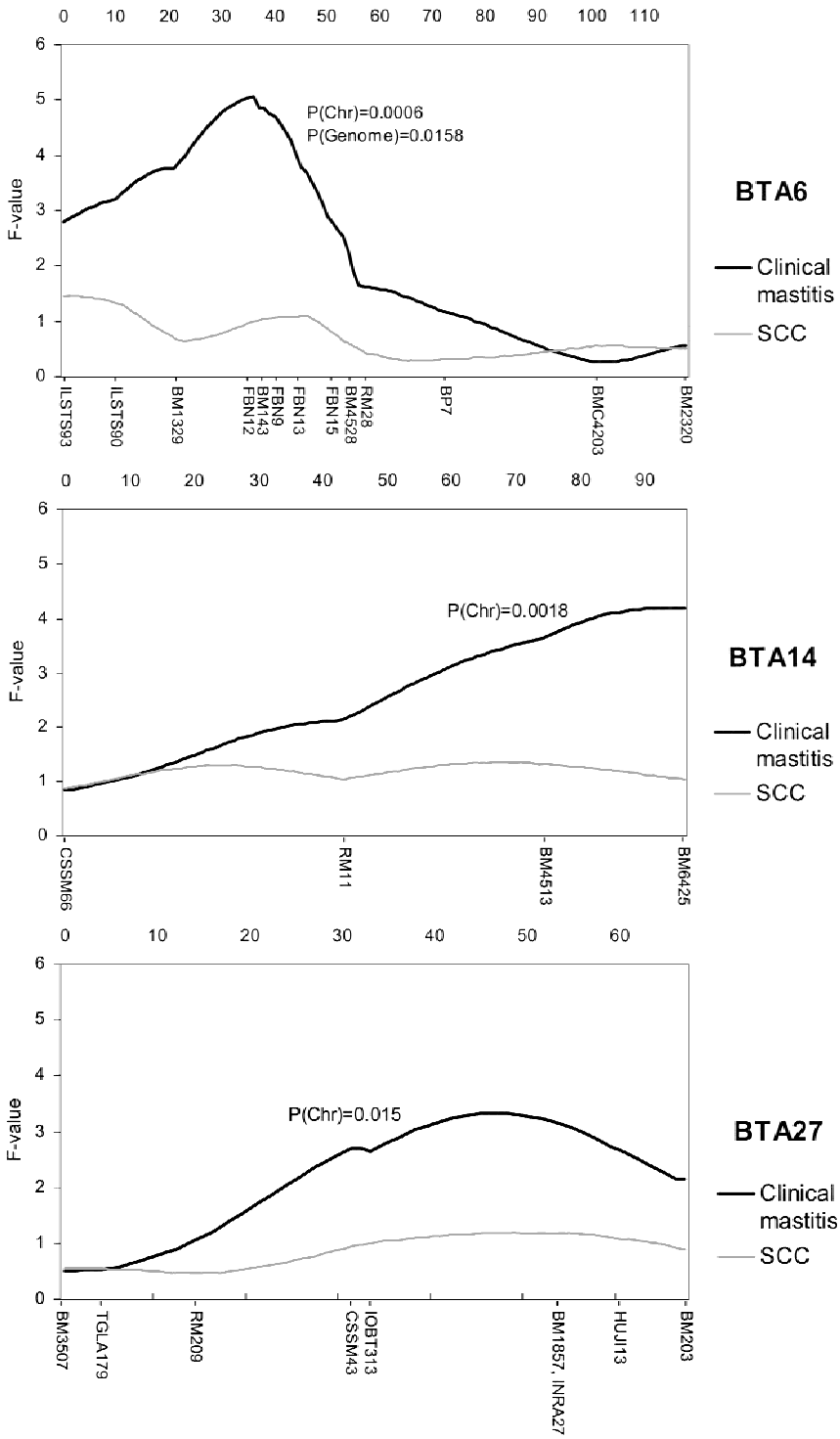

Fig. 1. Continued.

and 27; Fig. 1), of which one was genome-wise significant (Chr 6, Fig. 2).

The highest F-value (5.1) was observed for Chr 6 in position 37. This QTL was mainly caused by the contrast found within three families—2005, 2052, and 2463—which had individual F-values of 7.3, 12.8, and 9.0, respectively (Fig. 2). Confidence interval was calculated to 1–49 cM. Among the remaining putative QTL, all except one were mainly caused by the contrast found within a single family, or within two families. Family 3131 was involved in all these QTL findings, with additional effects from bullsires 2052 (BTA4) and 2402 (BTA14). The QTL on Chr 27 was caused by small effects in several families. As an example, the BTA14 QTL in position 93 (F-value 4.2) was composed of effects due to bull sires 2402 (F-value 14.5) and 3131 (F-value 8.9).

When SCC were analyzed, the results obtained for clinical mastitis could not, in any way, be reproduced. There were no obvious overlaps between the SCC QTL and the most promising QTL found for clinical mastitis (Fig. 1). A single QTL affecting SCC, which was chromosome-wise significant, was localized to Chr 8 (position 54, F-value 3.5). Although a maximum exists for clinical mastitis at the same location (Fig. 3), the effects were caused by different families. Whereas the SCC QTL was caused by

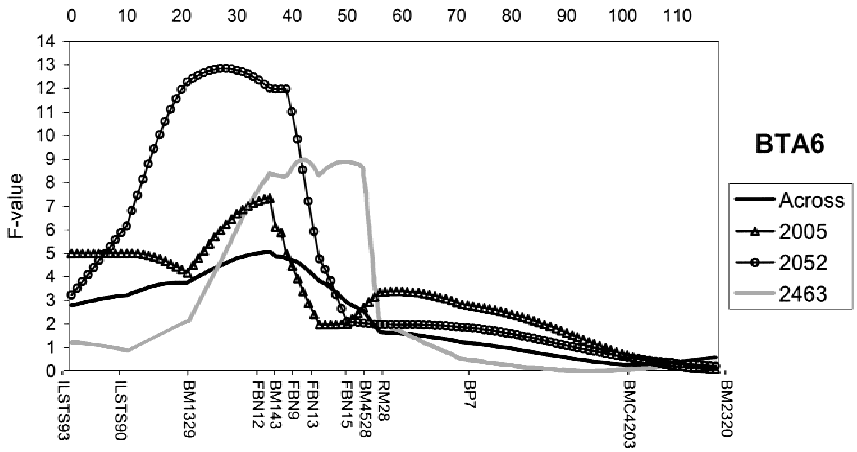

Fig. 2. Across- and within-family interval mapping of clinical mastitis for bovine Chr 6 (position 37, F-value 5.1), illustrating suggestive mastitis QTL produced by families 2005 (position 37, F-value 7.3), 2052 (position 29, F-value 12.9) and 2463 (position 42, F-value 9.0).

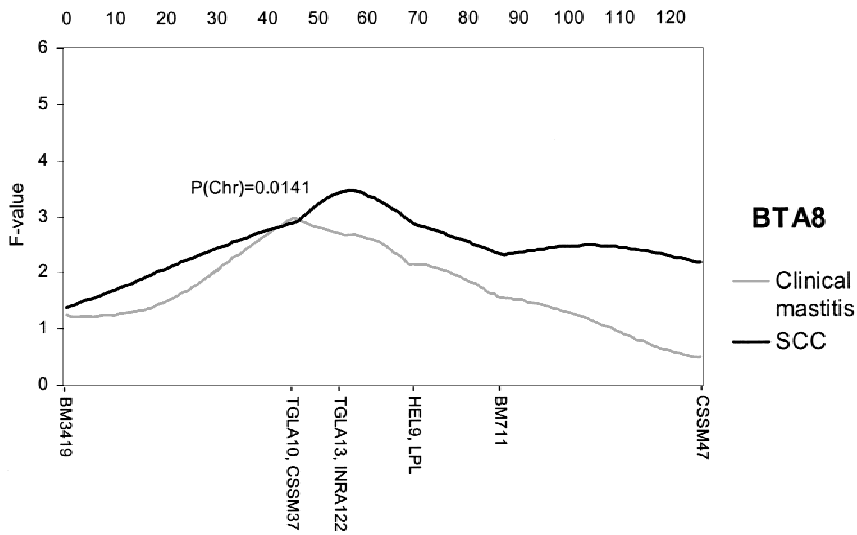

Fig. 3. A single QTL affecting somatic cell count (SCC), due to one family (2946, F-value 18.6), was localized to Chr 8 (position 54, F-value 3.5), whereas QTL for clinical mastitis was not significant (position 46, F-value 3.0) and has its origin in two other families (family 2402, F-value 7.0 and 3131, F-value 11.3).

a single family (Family 2946, F-value 18.6), the effect on mastitis was produced by families 2402 (F-value 7.0) and 3131 (F-value 11.3).

Discussion

Control of mastitis is of great importance to obtain cost-effective dairy production, for reducing the use of antibiotics, and for improving animal welfare. Hence, national recording, including all veterinary treatments on an individual animal basis, has been established in Norway. Since antibiotics can be prescribed only by veterinarians, these unique recordings are also very reliable. Furthermore, a high number of daughters per sire makes it possible to calculate breeding values with high accuracy also for low heritable traits like clinical mastitis. From this unique source, we have unveiled definite QTL for the most important health trait in dairy cattle. These results have a potential of being particularly useful through marker-assisted selection, especially in breeds or populations that are lacking historical registrations on mastitis.

As a result of the shortage of data on clinical mastitis, no QTL have so far been published for this trait. There are, however, quite a few recent papers that are focusing on SCC, of which the main part is from the Holstein population (Ashwell et al. 1996, 1997, 1998a; Reinsch et al. 1998; Schrooten et al. 2000; Zhang et al. 1998). Common for these studies are a relatively low number of QTL findings and mainly nonsignificant results. In one of these studies (Zhang et al. 1998), carried out in a large Holstein grand-daughter design, a QTL was localised to Chr 4, close to the *RM188* marker (Zhang et al. 1998). Although this QTL is not genome-wise significant, similar observations in two different studies, using different breeds, normally strengthen that location as a putative QTL. One should, however, be aware of the fact that clinical mastitis and SCC obviously monitor different aspects of udder health, as overlaps between these two traits did not exist in our study (see Figs. 1 and 3). Since the number of potential QTL is very high when single families are analyzed, and probably include several false positives, supplementary data are needed to verify QTL results.

Because detection of QTL is an inexact science, suggestive QTL should be verified in different populations. In the Finnish Ayrshire, a putative QTL for veterinary treatments has been localized to Chr 23 (Elo et al. 1999; see Table 2). However, the analyzed trait did not include treatments related to fertility or mastitis, and we did not observe similar results for mastitis in our study. Since the Finnish study included only Chr 23, comparisons with QTL found at other Chrs are not possible. QTL affecting health traits have also been found in US Holstein cattle (Ashwell et al. 1996, 1997, 1998a). Although 10 different chromosomes were included in these studies, the number of markers were limited to 16, of which 6 were positioned at Chr 23. The US Holstein cattle exhibit a potential SCC QTL at BTA 18, and within-family significant marker allele differences were also found at Chr 23 (Ashwell et al. 1996, 1997, 1998a). In several of these studies a limited selection of “candidate-chromosomes” have been ana-

lyzed, as Chr 23 that contains the BoLA complex. In a whole-genome scan of the North American Holstein-Friesian population, a suggestive SCC QTL was localized to Chr 21 (Heyen et al. 1999). This finding has no counterpart in our study.

Unfavorable genetic correlation between high milk production and increased frequency of mastitis is well known. It was, therefore, an expected result that some QTL affecting mastitis would be positioned close to QTL of milk production traits. A number of QTL affecting milk production traits have been published in different breeds, of which several map to Chr 6 (Ashwell et al. 1998b; Ashwell and Tassell 1999; Georges et al. 1995; Gomez-Raya et al. 1998; Kühn et al. 1999; Schrooten et al. 2000; Spelman et al. 1996; Velmala et al. 1999; Wiener et al. 2000). Hence, the milk BTA 6 QTL is segregating in both Holstein and Ayrshire populations, among these the NRF population (results not published). In NRF, the main families contributing to the BTA 6 mastitis QTL are 2005, 2052, and 2463 (Fig. 2). The QTL affecting milk yield is mainly found within 2463, which is significant, but with small additional effects also from other families. From these similar findings, it could be argued that the mastitis QTL is caused by high milk yield, rather than a change in the immune response. Alternatively, the colocalized QTL effects in family 2463, affecting both milk production and mastitis, could have a different genetic background from the QTL observed in 2005 and 2052. Position of the mastitis QTL in different families varies (Fig. 2), and a relatively large confidence interval could easily hold several independent QTL.

Several strategies have been proposed for confirming suggestive QTL (Georges 1999; Spelman and Bovenhuis 1998), including combinations of independent studies, also in different breeds, as described above. An alternative to this strategy is to establish confirmation studies (Spelman and Bovenhuis 1998). For further strengthening the results presented in this paper, we are now examining additional families that show high variation in the incidence of clinical mastitis. Included in this work is also collaboration with other Nordic countries that have similar records on clinical mastitis recorded in their dairy cattle breeds. Additionally, we also make use of a fine mapping strategy for characterizing the most promising QTL.

We have previously completed a mapping study with the bovine *Fc*γ*RI, II,* and *III* genes (Klungland et al. 1997). Comparable to the situation on human Chr 1, all these members of the leukocyte antigen family in cattle are clustered together in a region covering approximately 10 cM of Chr 3, the bovine homologous of human Chr 1. *Fc*γ*R* function includes binding and transport of IgG, phagocytosis, and antibody-dependent cellular cytotoxity (Barclay et al. 1993). Polymorphisms within the *Fc*γ*R* genes were used when localizing the QTL for mastitis on Chr 3. However, although the position of the BTA3 QTL is not well defined (Fig. 1), the position of the *Fc*γ*R* genes probably excludes them from being potential candidate genes for the variation in mastitis observed here.

Two methods for detailed characterization of potential QTL are positional cloning and the candidate gene approach. Although the fulfilment of the human genome project does not mean that the list of human protein-coding gene is complete, detailed studies of QTL are more likely to be a matter of testing candidate genes rather than discovering genes (Rikke and Johnson 1998). Since positions of QTL found for clinical mastitis are not yet sufficiently well defined, positional cloning will not be the method of choice. An alternative possibility is to use comparative QTL data, as discussed above for mastitis and SCC within the same species, or similar traits studied between species. Although the possibilities vary between species, there are examples of traits that have been studied in a number of species. One such trait is obesity, which is of great interest with regard to humans, to animal models, and to domestic animals (Chagnon et al. 2000). More than 40 candidate genes for obesity have been found, and some cases of obesity can now be explained by variation in specific genes. Although mastitis is of special interest for milk-producing animals, there is a potential to use this information in future studies on human mastitis, which is a serious and widespread problem that is difficult to address in humans.

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