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Confirmation of quantitative trait loci for somatic cell score on bovine chromosome 18 in the German Holstein

Abstract

Fifty-one half-sib families with 2768 sires were selected for this study to confirm a quantitative trait locus (QTL) detected within a previous project initiated by the German Cattle Breeders Federation (ADR). The data based on a granddaughter design were divided into two parts and were analysed using linear models and paternal half sib regression methods. The results strongly support the hypothesis that the chromosomal region around marker TGLA227 at the telomeric end of chromosome 18 harbours a QTL for somatic cell score (SCS) in the German Holstein population. Using a two-QTL model the analysis showed evidence for another QTL for SCS in that region on chromosome 18. Further fine mapping studies should be carried out to decide on the two QTL hypothesis.

Key Words: somatic cell score, German Holsteins, udder health, QTL, chromosome 18

Zusammenfassung

Titel der Arbeit: **Untersuchung zu Quantitativ Trait Loci für somatische Zellzahl auf dem bovinen Chromosom 18 bei Deutschen Holsteins unter Verwendung zweier Granddaughter-Designs**
Einundfünfzig Halbgeschwisterfamilien mit 2768 Söhnen wurden für eine Bestätigungsstudie selektiert. Die Daten auf Grundlage eines Granddaughter-Designs wurden in zwei Gruppen geteilt und mit linearen Modellen und paternalen Halbgeschwister-Regressionen analysiert. Das Ergebnis zeigt, dass der Marker TGLA227 in einigen Familien der Deutschen-Holstein-Population am Ende des Chromosoms 18 gekoppelt ist mit einem QTL für somatische Zellzahl (SCS). Unter Verwendung eines Zwei-QTL-Modells konnte ein Hinweis für einen weiteren QTL in diesem Bereich auf Chromosom 18 erbracht werden.

Schlüsselwörter: Somatische Zellzahl, Deutsche Holsteins, Eutergesundheit, QTL, Chromosom 18

Introduction

Somatic cell score (SCS) is a well known indicator trait for mastitis resistance and is implemented in the routine sire evaluation in many countries. Meanwhile, many quantitative trait loci (QTL) affecting SCS have been reported (http://www.vetsci.usyd.edu.au/reprogen/QTL_Map). In particular, the marker TGLA227 as well as other telomeric regions of BTA18 have repeatedly shown to harbour QTL for SCS (ASHWELL et al., 1997; SCHROOTEN et al., 2000; RODRIGUEZ-ZAS et al., 2002; BRINK, 2003; KÜHN et al., 2003; HOLMBERG and ANDERSSON-EKLUND, 2004; SCHULMAN et al., 2004). In the same region a genomewide significant QTL for clinical mastitis was detected (SCHULMAN et al.,

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2004). Additionally, on this chromosome QTL were identified for functional traits such as herd life, maternal and direct effect of dystocia, maternal and direct effect of stillbirth, and maternal and paternal effect of nonreturn rate of 90 days (KÜHN et al., 2003).

Before implementing a QTL in actual breeding schemes through marker assisted selection (MAS) in a certain population, it first has to be confirmed in the population due to uncertainty about the validity of the identified QTL and its segregation in the breeding population (SPELMAN and BOVENHUIS, 1998).

The aim of this study was to confirm the QTL for SCS on BTA18 in the German Holstein population reported by KÜHN et al. (2003) and to discover heterozygous families segregating for this QTL.

Materials and Methods
Animals and genotypes

Two different and distinct granddaughter designs (i.e. no overlap between the designs) were analysed consisting of altogether 2768 progeny tested German Holstein dairy cattle bulls. The bulls of the first granddaughter design were genotyped at the marker TGLA227 during routine parentage testing. Non-informative families, non-informative sires and sires involved in a conflict (i.e., TGLA227 homozygous grandsires, paternally inherited TGLA227 allele not identifiable, and violation of the Mendelian laws of inheritance, respectively) were excluded. The final size of this granddaughter design was 752 animals from 14 families; the average family size was 54 and varied from 30 to 114. This granddaughter design will be termed first data set in the following.

The animals of the second granddaughter design were genotyped at five microsatellite markers located on BTA18 (i.e., TGLA227, BM2078, BMS2639, ILSTS002 and BM7109). Conflicting sires were excluded from the data set. Finally, it consisted of 36 families with 2016 animals. The average family size was 56, ranging from 26 to 123. CRI-MAP was used to compute a genetic linkage map (GREEN et al., 1990). This granddaughter design will be termed second data set in the following.

Table 1
Number of records (N), means, standard deviation (Std.dev.), minimum and maximum for daughter yield deviations of somatic cell score and de-regressed breeding values of somatic cell score (Zahl der Beobachtungen (N), Mittelwerte (Mean), Standardabweichungen (Std.dev), Minimum und Maximum für durchschnittliche korrigierte Töchterabweichung für somatische Zellzahl und deregressierte Zuchtwerte für somatische Zellzahl)

Trait class	N	Mean	Std.dev.	Min.	Max.
DYD_{SCS-1L}	1946	0.0012	0.337	-0.832	1.425
DYD_{SCS-2L}	1515	0.0151	0.402	-2.069	1.601
DYD_{SCS-3L}	550	0.0083	0.402	-1.065	1.609
DG-RZS	2012	119.6354	15.545	65.909	182.456

DYD_{SCS-1L}, DYD_{SCS-2L}, DYD_{SCS-3L}: daughter yield deviations for 1., 2., 3. lactation; DG-RZS: de-regressed estimated breeding value of somatic cell score

Phenotypes

Phenotypes for both data sets were provided by the Vereinigte Informationssysteme Tierhaltung w.V. (VIT). Four classes of phenotypic data were available for the trait somatic cell score (SCS): daughter yield deviations for the first (DYD_{SCS-1L}), for the second (DYD_{SCS-2L}) and for the third lactation (DYD_{SCS-3L}) and, additionally, estimated breeding values (DG-RZS). The latter were de-regressed as described by THOMSEN

et al. (2001). Note that not all sires had an observation for each of the four SCS phenotypic classes, see Table 1. For the analysis of effects on other traits putatively linked to the SCS QTL, de-regressed estimated breeding values were used for five milk traits and eight functional traits (see KÜHN et al., 2003).

Statistical analysis

Both data sets were analysed by weighted linear models. The weighting factors were calculated for each phenotypic observation as described by SPELMAN et al. (1996) in order to account for the different number of daughters' contribution to the phenotype of the sire. The corresponding heritabilities were taken as for the routine sire evaluations (see http://www.vit.de).

The first data set was analysed by the following single marker model using the SAS GLM procedure (SAS Institute, Cary, NC):

$$y_{ij} = gs_i + m_{ik} + e_{ij},$$

where y_{ij} is the trait value of the jth son of the ith grandsire, gs_i is the fixed effect of the ith grandsire, m_{ik} is the fixed effect of the kth paternally inherited TGLA227 marker allele nested within grandsire i, and e_{ij} is the random residual.

The second data set was analysed by a multi-marker regression (KNOTT et al., 1996) using the following model:

$$y_{ijk} = gs_i + b_{ik} \times P_{ijk} + e_{ijk},$$

where y_{ijk} is the trait value of the jth son of the ith grandsire, gs_i is the fixed effect of the ith grandsire, b_{ik} is the regression coefficient for the ith grandsire at the kth chromosomal location, P_{ijk} is the probability of the jth son receiving the chromosomal segment of the first gamete from the ith grandsire at kth chromosomal position, and e_{ijk} is the random residual. The software package QTL Express (http://qtl.cap.ed.ac.uk), as described by SEATON et al. (2002), was used for the multi-marker regression. A chromosomewise significance threshold was determined by applying the permutation test with 10,000 permutations for the trait SCS and 1000 permutations for all other traits. Regression analysis was applied every cM along the chromosome.

Grandsires putatively heterozygous at the QTL for the trait SCS were identified by contrasting the two paternal half-sib groups with respect to their inheritance of the paternal TGLA227 marker allele (first data set) and with respect to their inheritance of the paternal haplotype at the estimated QTL position (second data set). The null hypothesis was that the grandsire was homozygous at the QTL, this was tested by a t-test, resulting in a pointwise error probability ($p_{pointwise}$) for each test conducted. This resulted in a multiple testing problematic, and for a chosen pointwise significance level it is expected that some tests are significant merely by chance. Therefore, the $p_{pointwise}$ were converted into experimentwise error probabilities ($p_{experimentwise}$) using the Bonferroni correction: $p_{experimentwise} = 1 - (1 - p_{pointwise})^m$, where m is the number of families for the respective SCS phenotypic class, with m = 43 for DYD_{SCS-1L}, m = 35 for DYD_{SCS-2L}, m = 14 for DYD_{SCS-3L} and m = 51 for DG-RZS, respectively. Additionally, the concept of the false discovery rate was applied to account for this multiple testing problem: the 51 tests (i.e. 51 families were tested for QTL

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segregation) were ordered according to their $p_{pointwise}$ and then for each test a q value was estimated as described by BENJAMINI and HOCHBERG (1995). The q value of a particular test i can be interpreted as the false discovery rate if all tests with lower or equal $p_{pointwise}$ compared to the test i are defined as significant. The heterozygous families are shown in Table 3.

Additionally, for the trait somatic cell score a two-QTL model implemented in a grid search using QTL Express was fitted to the second data set as follows:

$$y_{ijk1k2} = gs_i + b_{ik1} \times P_{ijk1} + b_{ik2} \times P_{ijk2} + e_{ijk1k2},$$

where $k1$ and $k2$ refer to the position of the first and second QTL. Other terms are as defined in the one-QTL model. The minimum distance between the first and second investigated chromosomal position was set to 4 cM.

Results

The analysis of the first data set revealed a significant effect of the marker TGLA227 for the phenotypic classes DYD_{SCS-1L} ($p_{pointwise} = 0.0196$), DYD_{SCS-2L} ($p_{pointwise} = 0.0438$), DYD_{SCS-3L} ($p_{pointwise} = 0.0291$) and DG-RZS ($p_{pointwise} = 0.0271$). Hence, the existence of a QTL for SCS near to the marker TGLA227 is confirmed. Within segregating families no consistent QTL-marker haplotype could be observed.

The genetic map estimated from the second data set covers 43 cM (see Table 2 for further information). The marker order is in correspondence to previously published marker maps (HEYEN et al., 1999, VÅGE et al., 2000, THOMSEN et al., 2000, VIITALA et al., 2003).

Table 2
Genetic map and marker information (Genetische Karte und Markerinformationen)

Marker	BM7109	ILSTS002	BMS2639	BM2078	TGLA227
Relative position cM	0.0	10.9	13.0	34.5	43.0
Informative meioses	991	966	1381	1397	1549
Heterozygous grandsires*	26	26	32	32	33
Alleles	10	8	9	10	11

*36 sires genotyped for BM7109, ILSTS002, BMS2639 and BM2078, 35 sires genotyped for TGLA227

For all four phenotypic classes a QTL was mapped at position 43 cM. The plot of the test statistic along the considered chromosomal region is shown in the Figure. The traits DYD_{SCS-2L} and DG-RZS reached the 10% chromosomewise significance level across all families. The results of the individual family analysis are shown in Table 3. For all other analysed traits only a highly significant QTL effect for udder depth was detected at position 30 cM ($p_{chromosomewise} = 0.01$) across all families.

The results of the two-QTL model of the second data set revealed a peak in the test statistic at positions 34 and 43 with an error probability of $p_{pointwise} = 0.0215, 0.0246, 0.0571$ and 0.1030 for DG-RZS, DYD_{SCS-2L}, DYD_{SCS-1L} and DYD_{SCS-3L}, respectively (two QTL vs no QTL) and $p_{pointwise} = 0.1437, 0.1782, 0.2993$ and 0.2703 for DG-RZS, DYD_{SCS-2L}, DYD_{SCS-1L} and DYD_{SCS-3L}, respectively (two QTL vs one QTL). The grandsires putatively heterozygous at the QTL are listed in Table 4. Here no correction for multiple testing was performed as these results should only be used as an indicator for a second putative QTL on BTA18 rather than a statistical proof for the existence of a second QTL. Therefore, no sophisticated model comparison was conducted, either.
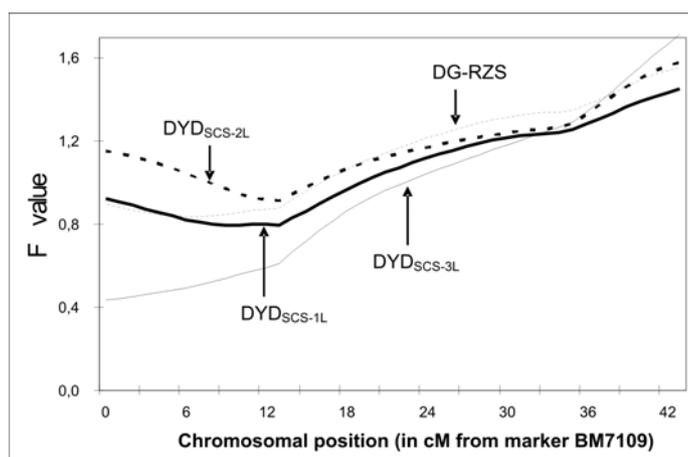
Figure: Plot of the test statistic along the considered chromosomal region of BTA18
DYD_{SCS-1L}, DYD_{SCS-2L}, DYD_{SCS-3L}: daughter yield deviations for 1st, 2nd, 3rd lactation; DG-RZS: de-regressed estimated breeding value of somatic cell score. For the marker positions see Table 2.
(Plot der Teststatistik im Bereich der untersuchten Region von BTA18)

Table 3
Pointwise and experimentwise error probabilities, FDR-q values for the most significant families for QTL position 43 cM, results from the one-QTL model and both data sets (Punktweit und experimentweit Irrtumswahrscheinlichkeiten, FDR-q Wert für die signifikantesten Familien QTL-Effekt, p- und q-Werte in signifikanten Familien für QTL-Position in der Nähe des Markers TGLA227, Ergebnisse des Ein-QTL-Modells und beiden Datensätzen)

Trait class	Family	$p_{pointwise}$	$p_{experimentwise}$	FDR-q value
DG-RZS (m = 51)	44	0.0017	0.0831	0.0867
	4	0.0083	0.3469	0.2121
	35	0.0202	0.6469	0.3435
	8	0.0275	0.7590	0.3508
	2	0.0402	0.8764	0.3663
	48	0.0475	0.9164	0.3663
	21	0.0503	0.9280	0.3663
	28	0.0779	0.9840	0.4644
	49	0.0937	0.9934	0.4644
DYD_{SCS-1L} (m = 43)	8	0.0018	0.0743	0.0495
	44	0.0023	0.0943	0.0495
	4	0.0058	0.2198	0.0825
	21	0.0397	0.8252	0.4273
	2	0.0728	0.9612	0.6259
	28	0.0877	0.9807	0.6283
DYD_{SCS-2L} (m = 35)	44	0.0023	0.0774	0.0779
	4	0.0054	0.1722	0.0779
	8	0.0067	0.2090	0.0779
	35	0.0237	0.5687	0.2078
	12	0.0884	0.9609	0.5460
DYD_{SCS-3L} (m = 14)	44	0.0015	0.0208	0.0210
	8	0.0288	0.3356	0.2015
	4	0.0915	0.7390	0.3692

DYD_{SCS-1L}, DYD_{SCS-2L}, DYD_{SCS-3L}: daughter yield deviations for 1., 2., 3. lactation; DG-RZS: de-regressed estimated breeding value of somatic cell score; m: number of families
The QTL effects from family 1 to 37 were estimated by QTL Express, family 38 to 51 by SAS GLM analysis. p, q and p_B are the p-value, false discovery rate and Bonferroni p-value, m is the number of families

Table 4
Pointwise error probabilities for the families with a significant QTL at position 34 cM (P1) and position 43 cM (P2), results from the two-QTL model and second data set (Punktweite Irrtumswahrscheinlichkeitseffekt an chromosomaler Position 34 cM (P1) und 43 cM (P2), Ergebnisse des Zwei-QTL-Modells und des zweiten Datensatzes)

Family	DG-RZS		DYD$_{SCS-1L}$		DYD$_{SCS-2L}$		DYD$_{SCS-3L}$	
	P1	P2	P1	P2	P1	P2	P1	P2
2	0.4322	0.6146	**0.0910**	0.1334	—	—	**0.0955**	0.1106
4	0.8949	0.1227	0.7234	0.2062	0.2846	<u>**0.0140**</u>	0.8779	0.6203
6	0.8428	0.6216	0.6651	0.4269	<u>**0.0299**</u>	<u>**0.0159**</u>	—	—
8	0.5345	0.9297	0.8037	0.4731	0.6387	***0.0064***	0.9489	0.5728
16	**0.0531**	0.1163	0.1466	0.2159	0.8298	0.8645	0.3684	0.4832
19	0.4864	0.3678	0.3894	0.3576	0.5402	0.7746	0.1368	**0.0862**
21	0.6641	0.1113	0.5776	**0.0773**	0.9655	0.2477	—	—
22	0.2823	0.2207	<u>**0.0338**</u>	<u>**0.0276**</u>	0.4793	0.2158	—	—
24	<u>**0.0143**</u>	**0.0523**	**0.0512**	**0.0629**	0.4575	0.6289	—	—
25	<u>**0.0166**</u>	<u>**0.0324**</u>	**0.0362**	0.1013	<u>**0.0216**</u>	0.2426	—	—
27	0.1629	0.1626	**0.0720**	**0.0700**	—	—	—	—
28	0.5264	0.2530	0.6092	0.3113	0.2561	**0.0999**	—	—
34	<u>**0.0302**</u>	**0.0672**	**0.0745**	0.1058	<u>**0.0382**</u>	0.9591	—	—
35	0.6859	<u>**0.0388**</u>	0.8037	0.2023	0.4002	<u>**0.0233**</u>	—	—
37	**0.0246**	**0.0343**	**0.0373**	<u>**0.0231**</u>	0.0557	<u>**0.0157**</u>	**0.0580**	<u>**0.0141**</u>

DYD$_{SCS-1L}$, DYD$_{SCS-2L}$, DYD$_{SCS-3L}$: daughter yield deviations for 1., 2., 3. lactation; DG-RZS: de-regressed estimated breeding value of somatic cell score
Bold numbers reach a 10% pointwise significance; bold numbers with underline reach a 5% pointwise significance; and bold numbers in italics reach a 1% pointwise significance

Discussion

Several studies have reported QTL for SCS on chromosome 18: between BM7109 and ILSTS002 (SCHROOTEN et al., 2000), between BMS2639 and TGLA227 (SCHULMAN et al., 2004), between BMS1355 and TGLA227 (HOLMBERG and ANDERSSON-EKLUND, 2004), and at TGLA227 (KÜHN et al., 2003; SCHULMAN et al., 2004). ASHWELL et al. (1997) found a QTL for SCS near microsatellite marker BM2078 corresponding to the position of 34.5 cM in our study, though the authors were unable to reproduce it in ASHWELL et al. (2004). In our study, the highest test statistic of the analysis of the second data set for all four SCS phenotypic classes was found at the chromosomal position of marker TGLA227 at 43 cM. The existence of the SCS QTL is therefore confirmed at this chromosomal position in the German Holstein dairy cattle population, especially since both data sets analysed are independent and showed significant SCS-QTL effects at marker TGLA227. The families putatively heterozygous at the QTL (Table 3) can be used for further investigations regarding SCS. Thereby the inferences should be made using either the DYD$_{SCS-1L}$ or the DR-RZS phenotypic class due to a potential selection bias when using solely phenotypes from higher lactations.
The results of the two-QTL model applied to the second data set revealed a second putative SCS QTL next to marker BM2078, where ASHWELL et al. (1997) reported an SCS QTL. Interestingly, some families showing no significant marker effects, when the one-QTL model was used, do so with a two-QTL model. In these families the two QTL have effects of similar quantity but with an opposite sign. This suggests that the two QTL effects oppose each other, so that these families appeared to be QTL

homozygous in the one-QTL model. The results indicate that there could be another QTL at 34 cM in the same range of chromosome 18. SCHULMAN et al. (2004) did not fit a two-QTL model for SCS because they had no indication of two separate QTL positions on the same chromosome; ASHWELL et al. (2004) found no evidence favouring a two-QTL- over a one-QTL model in their whithin- and across-family analyses for SCS.

The QTL transition probabilities at position 34 might also be determined by the marker TGLA227 (multi-marker approach), hence the QTL at this position could be a shadow effect of the QTL at TGLA227 rather than a real second QTL. However, the impact of TGLA227 on the QTL transition probability at 34 cM might be only small, because marker BM2078 is very informative itself. Additionally, different families segregated at both QTL using the 2-QTL model (Table 4), which can be interpreted against a shadow effect of the TGLA227 QTL. BRINK (2003) reported two peaks for the QTL of SCS at positions 88 cM and 122 cM, corresponding to 16 cM and 43 cM in our study, respectively. In the study of BRINK (2003) a denser marker map was used and, therefore, the possibility of shadow effects was almost excluded.

The QTL effect for udder depth at position 30 cM could be due to the correlation of this trait with SCS (LUND et al., 1994).

Several studies (e.g., GOLDAMMER et al., 2002; BRUNNER et al., 2003) have reported that the telomeric region of BTA18 exhibits high similarity to the HSA19q region in humans, that contains several gene families with effect on the immune system such as the *SIGLEC-* (sialic acid binding Ig-like lectin), the KIR- (killer cell immunoglobulin-like receptor) and the *LILR* (leukocyte immunoglobulin-like receptor) gene clusters. For the peak at 34 cM, there are a lot of these above mentioned genes possibly suitable as candidates for further studies.

From comparative genome analysis, we still do not know any candidate genes near the marker TGLA227 except of *A1BG* showing homology to the immunoglobulin-family (ISHIOKA et. al, 1986). This gene is a ligand of *CRISP3* (UDBY et al., 2004), a gene involved in innate immunity (UDBY et al., 2002).

Conclusion

A one-QTL and two-QTL model were applied to the data provided for this study. The results strongly support the hypothesis that the marker TGLA227 is linked to a QTL for SCS segregating in German Holstein population in some half-sib families. The two-QTL analysis revealed the possibility of a second QTL for SCS in the same chromosomal region. Finemapping the QTL for SCS in the specific region of BTA18 might resolve the question if the two QTL hypothesis is correct.

Acknowledgements

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