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A Genome Scan To Identify Quantitative Trait Loci Affecting Economically Important Traits in a US Holstein Population

M. S. Ashwell, C. P. Van Tassell, and T. S. Sonstegard
Agricultural Research Service, USDA, Beltsville, MD 20705

ABSTRACT

Quantitative trait loci affecting economically important traits were studied for eight large US Holstein grandsire families by using the granddaughter design. A total of 155 microsatellite markers located throughout the bovine genome were selected for the scan. The data analyzed include genotypes for 50 markers not previously reported. Results analyses of 105 marker genotypes reported previously were updated. Effects of marker alleles were analyzed for 38 traits including traits for milk production, somatic cell score, productive life, conformation, calving ease, and 16 canonical traits derived from conformation and production traits. Permutation tests were used to calculate empirical traitwise error rates. A traitwise critical value of $P = 0.1$ was used to determine significance. Ten putative quantitative trait loci associated with seven of the new markers were identified within specific families. One marker on chromosome 14 was associated with differences in fat yield, fat percentage, and a canonical production trait in two families. Markers on chromosomes 18 and 22 were associated with differences in rump angle in the same family. Markers were associated with differences in udder depth and fore udder attachment on chromosomes 16 and 20, respectively. One marker on chromosome 27 was associated with a difference in the dairy capacity composite index, and another marker on chromosome 13 was associated with a difference in a canonical conformation trait. These additional markers complete our genome scan to identify quantitative trait loci affecting economically important traits in a selected commercial Holstein population. The quantitative trait loci identified in this genome scan may be useful for marker-assisted selection to increase the rate of genetic improvement on traits such as disease resistance and conformation traits associated with fitness while accelerating genetic improvement for production.
(**Key words:** quantitative trait loci, microsatellite markers, conformation traits, milk production traits)

Abbreviation key: BTA = *Bos taurus* autosome; **DBDR** = Dairy Bull DNA Repository; **DD** = daughter deviation; **GSD** = genetic standard deviation; **MS** = microsatellite; **QTL** = quantitative trait loci; **PL** = productive life; **STA** = standardized PTA.

INTRODUCTION

Tradition selection methods have been effective at improving milk production in dairy cattle. In the US, milk production more than tripled, from 1940 to 1991, with fewer cows. Traditional selection methods used in the United States have not been as successful for traits such as reproduction and disease resistance, most likely due to the low heritabilities for these traits, the lack of data on which to base selection decisions, and the lack of selection pressure on these traits. In fact, incidences of disease and reproductive difficulty are more frequent (Hansen, 2000). In the last decade, studies have been conducted to identify genes affecting these economically important traits in commercial dairy populations.

In 1990, Weller et al. proposed a new experimental design, called the granddaughter design, for detection of quantitative trait loci (**QTL**). This design was ideal for detection of QTL in dairy populations due to the existence of large half-sib families, created through the heavy use of artificial insemination and the large amount of phenotypic information routinely collected and available through DHIA.

The first study illustrating the ability of the granddaughter design to detect QTL affecting milk production traits was published in 1995 (George et al., 1995). Since that time, results from many genome scans have reported putative QTL affecting milk production, health, conformation, and reproduction in different dairy populations by using a variety of statistical methods (Arranz et al., 1998; Georges et al., 1995; Heyen et al., 1999; Riquet et al., 1999; Schrooten et

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Corresponding author: M. S. Ashwell; e-mail: Mashwell@anri.barc.usda.gov.

al., 2000; Spelman et al., 1996; Van Tassell et al., 2000; Zhang et al., 1998). To date, there has been little consensus in the QTL mapping community on how data from QTL studies should be analyzed and what significance thresholds should be used to detect and report QTL. Therefore, it is not surprising that results from these studies sometimes confirmed the same QTL and, in other cases, provided conflicting results.

Here, results are presented from a genome scan comprised of 155 microsatellite markers to identify QTL affecting milk production, health, conformation, and reproduction in commercial dairy cattle. For 105 of these markers previously reported (Van Tassell et al., 2000), effects are updated with current estimates of genetic merit.

MATERIALS AND METHODS

Source of Materials

Semen samples from eight large Holstein families were selected from the Dairy Bull DNA Repository (**DBDR**; Da et al., 1994), as previously described (Ashwell et al., 1996). Data for milk yield and composition, SCS and productive life (**PL**) collected through August 2000 were provided by DHIA and processed as part of the routine genetic evaluation procedure by the Animal Improvement Programs Laboratory of ARS. Conformation trait data from the August 2000 genetic evaluation were provided by the Holstein Association USA (2000). Composite indices (udder, feet and legs, dairy capacity, and body form) were used as defined by the Holstein Association USA (2000). In addition, PTA from a National Association of Animal Breeders calving ease evaluation for August 2000 were obtained.

The 155 microsatellite (**MS**) markers used in this study were selected from the USDA bovine linkage map (Bishop et al., 1994; Kappes et al., 1997) or newly developed in our laboratory (Sonstegard et al., 2000a,b) as previously described (Van Tassell et al., 2000). Marker information was previously described for 105 of the 155 MS markers (Van Tassell et al., 2000). Information for the latest 50 MS markers analyzed here is given in Table 1. Amplification of these markers was performed by using fluorescent primers as previously described (Ashwell et al., 1997).

Statistical Analysis

Data from a total of 38 traits were analyzed in this study as previously described (Van Tassell et al., 2000). These traits included standardized PTA (**STA**) for 17 linear conformation traits, four composite indices, and PTA for final score; PTA and daughter deviation (**DD**) for milk, fat, and protein yield, fat and protein percentage, SCS, and PL; and expected progeny difference and expected percent difficult birth for calving ease. Trait data were analyzed for marker effects within each heterozygous grandsire family by using single-trait analysis implemented by PROC MIXED of SAS (SAS Institute, 1989) and described by Van Tassell et al. (2000). Trait wise empirical P values (noted as P_e) were obtained by using data permutation techniques based on the approach of Churchill and Doerge (1994) and described by Van Tassell et al. (2000). A critical value of 0.1 was chosen for the P_e values to guard against high type II error rates, i.e., to prevent missing true QTL because of conservative tests. In addition, because the DBDR is a highly selected population, the statistical power is already reduced in this experiment compared with using a random group of sons in these families (Georges et al., 1995). An additional threshold for suggestive significance of $P_c < 0.05$ was used when evaluating additional traits when a significant association was identified in a family for a marker. This same threshold was also used to evaluate families when a trait association was identified for a marker-trait combination across families. Note that the use of this term here is not as that described by Lander and Kruglyak (1995).

RESULTS AND DISCUSSION

A genome-wide scan has been completed in eight DBDR families to identify putative QTL affecting economically important traits. The scan generated a total of 55,589 unique genotypes from 155 markers on the 29 bovine autosomes. Table 1 details the information content for the latest 50 marker genotypes analyzed, whereas genetic information generated from the previous 105 markers was reported elsewhere (Van Tassell et al., 2000).

The average heterozygosity index for the 155 selected MS markers was 60.75% for the eight DBDR grandsires. Transmission of the grandsire alleles could be determined in only 68.9% of the sons from heterozygous grandsires in the absence of maternal genotypic data.

Results for within- and across-family analyses are given in Tables 2 and 3, respectively, in which analyses were conducted for all 155 MS markers by using the August 2000 estimates of genetic merit. Only effects with an empirical traitwise P value of <0.1 are reported. For completeness, results for comparisonwise (i.e., nominal) P value (P_c) and an empirical traitwise P value (P_e) are reported. Tests by using the P_c and P_e values identified very similar marker-trait associations by using thresholds of $P_c < 0.001$ and $P_e < 0.1$.

Table 1. Map position and informativeness for 50 microsatellite markers based on genotypes for all available sons of eight Dairy Bull DNA Repository families.

Chromosome	Relative position	Locus	Alleles	Heterozygous grandsires	Sons genotyped	Informative sons	Informative sons
	(cM)			(no.)			(%)
1	90	BB704	3	5	714	420	58.8
3	45.2	BL41	3	5	79	49	62.0
7	87	BB719	6	4	385	326	84.7
8	77.3	BB703	5	5	611	477	78.1
10	46.5	BM875	3	4	64	34	53.1
11	90.9	BL1103	5	4	462	382	82.7
	108.7	BMS655	3	4	549	322	58.7
12	15.1	BMS2252	4	5	605	454	75.0
	40.2	TGLA28	5	6	917	725	79.1
	56	BM6404	7	7	939	807	85.9
13	0	TGLA23	4	4	537	353	65.7
	19.5	BMC1222	6	6	100	85	85.0
	38.6	BM720	7	7	115	97	84.3
	49.5	UWCA25	3	7	983	628	63.9
14	6.2	BMS1678	4	8	1140	781	68.5
	26.7	BMS1941	5	8	981	744	75.8
	52	BMS1899	5	4	478	402	84.1
15	15	BB702	5	4	483	295	61.1
	68.8	BMS812	6	5	733	609	83.1
16	11.5	BB717	3	3	357	187	52.4
	11.5	HUJ614	3	3	320	198	61.9
	28.6	BM4025	6	6	560	467	83.4
	60.3	BB709	5	8	954	743	77.9
	93.2	BMS462	4	5	626	376	60.1
17	0	BB718	2	2	225	113	50.2
	3.8	BMS499	5	7	948	733	77.3
	30.1	BMS941	6	6	788	612	77.7
18	10.8	ILSTS021	3	4	480	346	72.1
	61	BB710	5	6	773	541	70.0
	63.3	BMS929	2	5	532	267	50.2
19	15.9	HEL10	2	1	170	86	50.6
	65.7	CSSM65	4	6	711	452	63.6
	78.6	IDVGA44	4	5	540	357	66.1
20	23.3	RM310	4	6	800	576	72.0
	45.5	BMS2361	5	4	460	344	74.8
	69	AFR2215	5	5	587	459	78.2
22	5.9	BMS672	3	3	413	234	56.7
	61.1	BMS875	3	6	641	439	68.5
	81.1	BM4102	4	5	557	417	74.9
23	7.2	CSSM5	4	5	751	619	82.4
	36.7	BB705	2	2	171	82	48.0
24	27.6	AGLA269	3	4	602	446	74.1
	46.5	BMS1332	4	5	531	374	70.4
	62.5	BMS3024	4	4	402	219	54.5
25	64.9	BM1864	2	3	440	272	61.8
27	15	BB716	2	2	252	113	44.8
	46.3	BB708	2	2	292	150	51.4
28	35.8	BM6466	6	6	817	669	81.9
29	19.7	BMC8012	5	6	77	57	74.0
	61	BMS1948	4	6	744	543	73.0

Based on our findings from the 50 additional markers, we have identified 10 new putative QTL within families (Table 2). These QTL include marker associations with fat yield, fat percentage, udder depth, rump angle, fore udder attachment, and the dairy capacity composite index. Two associations were identified for canonical traits, one for a conformation trait, and another for a production trait.

On bovine chromosome 14 (**BTA14**), BMS 1678 provided evidence for an important QTL affecting fat percentage and fat yield in families 1 and 4. Similar findings were reported by Heyen et al. (1999) with different markers from the same genomic region. In the Heyen et al. (1999) study, associations between the markers and fat percentage were highly significant in families 4 and 5 ($P = 1 \times 10^{-12}$ and 1×10^{-9}, respectively). There

were no significant associations with any traits in family 5 in our analysis, which may be due to differences in information content between marker genotypes in this genomic region. Riquet et al. (1999) have also reported a QTL affecting milk production and fat percentage in this region of BTA14 and have narrowed the interval containing the QTL to approximately 5 cM.

The majority of the new putative QTL reported here are associated with conformation traits. An association with BB709 and BTA16 was detected in family 8 for udder depth. The estimated difference between the genetic values of the two alleles was 1.12 genetic standard deviations (**GSD**). This marker had a suggestive association (P_c = 0.0026) for the udder composition index of which udder depth is a component. Another association with an udder conformation trait was detected with BMS2361 on BTA20 in family 4 for fore udder attachment. The estimated allelic difference was 0.73 GSD. This marker had suggestive associations for udder depth (P_c = 0.003) and the udder composite index (P_c = 0.001) that were not significant by using the traitwise error. In contrast, a similar study by Schrooten et al. (2000), to identify QTL affecting conformation and functional traits in dairy cattle, did not detect either of these two putative conformation QTL.

Two significant associations for rump angle were detected in family 2 on different chromosomes. The first significant association was detected with BB710 on BTA18, with an estimated allelic difference of 0.8 GSD. This marker had suggestive associations for many other conformation traits, with differences that

Table 2. Significant empirical traitwise (P_e < 0.1) marker effects within Dairy Bull DNA Repository (DBDR) family.

Chromosome	Marker[1]	Trait	DBDR family	Marker allele differences[2]	SE	Comparisonwise *P* value (P_c)	Empirical traitwise *P* value (P_e)
4	BL21	Teat length	3	–0.83	0.22	0.0002	0.090
5	BM43	Canonical conformation trait 4	5	1.38	0.35	0.0001	0.096
	BMS1248	Canonical conformation trait 12	12	2.01	0.46	<0.0001	0.045
6	BM1236	DD % protein	9	–0.057	0.013	<0.0001	0.015
	BM1236	Canonical conformation trait 10	8	–1.03	0.27	0.0002	0.100
	BM415	DD % protein	9	0.053	0.012	<0.0001	0.023
	BP7	PTA % protein	9	–0.044	0.010	<0.0001	0.014
7	BM6117	PTA SCS	1	–0.099	0.023	<0.0001	0.037
9	BMS1290	Rump angle	1	–0.75	0.18	<0.0001	0.025
	UWCA9	Canonical production trait 2	4	0.23	0.06	0.0001	0.067
13	**UWCA25**	Canonical conformation trait 9	8	0.98	0.24	<0.0001	0.040
14	BM6425	PTA % protein	9	–0.055	0.011	<0.0001	0.0005
	BM302	Front teat placement	12	1.38	0.34	<0.0001	0.040
	BM302	Fore udder attachment	12	1.27	0.32	0.0001	0.073
	BMS1678	DD Fat	4	11.86	2.07	<0.0001	0.001
	BMS1678	DD % Fat	4	0.086	0.021	<0.0001	0.035
	BMS1678	DD % Fat	1	–0.066	0.016	<0.0001	0.036
	BMS1678	Canonical production trait 3	1	0.25	0.054	<0.0001	0.001
16	**BB709**	Udder depth	8	–1.12	0.29	0.0002	0.099
18	**BB710**	Rump angle	2	0.80	0.19	<0.0001	0.028
20	**BMS2361**	Fore udder attachment	4	–0.73	0.19	0.0001	0.082
22	**BMS875**	Rump angle	2	0.88	0.20	<0.0001	0.008
23	BM1818	Canonical conformation trait 8	1	1.07	0.26	<0.0001	0.071
27	**BB716**	Dairy capacity composite index	2	0.82	0.20	<0.0001	0.051
	BMS1385	Dairy form	2	0.85	0.21	<0.0001	0.031

[1]Results for markers in boldface are first reported here in this study.

[2]Units of marker allele differences (smaller sized allele minus larger sized allele, measured in basepairs): PTA or daughter deviation (DD) milk, fat, protein yield reported in kg; SCS adjusted to log base 2 of the concentration; % protein and fat reported as % of protein or fat yield/milk yield; productive life reported as months of life, limited to 7 yr; and 10 mo of life/lactation; conformation traits as units of genetic standard deviation; canonical traits are units of transformed traits.

Table 3. Significant empirical traitwise ($P_e < 0.1$) marker effects across families.

Chromosome	Marker[1]	Trait	Comparisonwise P value (P_c)	Empirical traitwise P value (P_e)	Families (no.)
2	BM1223	Canonical conformation trait 9	0.0003	0.044	2
3	BMS482	PTA % protein	0.0006	0.092	7
4	MAF70	Body depth	0.0005	0.095	4
	MAF70	Strength	0.0002	0.029	4
5	BM43	Dairy form	0.0006	0.066	7
6	BM1236	DD % protein	<0.0001	0.020	6
	BM415	PTA % protein	<0.0001	0.009	6
	BP7	PTA % protein	0.0004	0.057	5
	BM1236	Canonical production trait 4	<0.0001	0.018	6
9	BMS1290	Rump angle	<0.0001	0.001	6
	BMS1290	Canonical conformation trait 6	0.0001	0.022	6
	BMS1943	Canonical conformation trait 6	0.0003	0.055	6
12	**BM6404**	Foot angle	<0.0001	0.010	7
	BM6404	PTA type	0.0003	0.053	7
	BM6404	Feet and leg composite index	0.0004	0.069	7
	BM6404	Rear legs-rear view	0.0006	0.073	7
14	**BMS1678**	DD fat	<0.0001	0.001	8
	BMS1678	DD % fat	<0.0001	0.001	8
	BMS1678	Canonical production trait 3	<0.0001	0.001	8
	BM6425	PTA % protein	<0.0001	0.016	7
15	**BMS812**	Canonical conformation trait 1	<0.0001	0.014	5
16	**BB709**	Udder depth	0.0001	0.015	8
	BB717	Canonical conformation trait 6	0.0003	0.052	2
18	**ILSTS021**	Canonical conformation trait 9	0.0001	0.026	4
20	**BMS2361**	DD % protein	0.0003	0.053	4
23	**BB705**	Rear legs-side view	0.0006	0.085	2
27	BMS1385	Dairy form	0.0004	0.050	4
	BB716	Dairy capacity composite index	0.0004	0.058	2
28	BM2515	PTA % protein	0.0004	0.066	3

[1]Results for markers in boldface are first reported here in this study.

were not significant using the traitwise error, including STA for body depth ($P_c = 0.001$), stature ($P_c = 0.008$), strength ($P_c = 0.002$), thurl width ($P_c = 0.002$), and body form composite index ($P_c = 0.002$). The other significant association in this family was detected with BMS875 on BTA22, with an estimated allelic difference of 0.88 GSD. This marker also had suggestive associations for other conformation traits including stature (P_c = 0.0007) and canonical conformation trait 5 (P_c = 0.0009). Again, these putative QTL were not detected in the study by Schrooten et al. (2000).

On BTA27, BB716 provided evidence of a QTL affecting the dairy capacity composite index in family 2. Previously, we failed to report a putative QTL affecting dairy form in family 2 on BTA27 with marker BMS1385 (Van Tassell et al., 2000), which is approximately 6 cM from BB716. The dairy capacity composite index is calculated from the dairy form and strength trait values, so it is likely that this association detected the same dairy form QTL we previously reported. Schrooten et al. (2000) reported a suggestive QTL affecting udder depth in the same region of this chromosome, which may be associated with the dairy form QTL.

Only one canonical conformation trait was significantly associated with the latest markers evaluated in this study. Marker UWCA25 on BTA13 was associated with canonical conformation trait 9 ($P_c < 0.0001$ and P_e = 0.040). This trait is derived from all 17 linear conformation traits with approximately 62% of the weight given to rear legs-side view. Despite this weight on a leg trait, none of the individual conformation traits approached significance with this marker.

Of the 10 new significant marker-trait associations found within families, five were also significant in the across-family analysis (Table 3). However, in all but one (BB716 dairy capacity composite index) of these five, other families were significant at a suggestive level ($P_c < 0.05$). Nine other newly identified marker-trait associations were significant in the across-family analysis but were not significant within any specific family at $P_e < 0.1$. Each of these marker-trait associations will now be considered. In the case of four of these associations (BMS812, BB717, ILSTS021, and BB705), significant results from only one family were enough to detect a traitwise significance in the across-family analysis. Results for BM6404 on BTA12 for foot angle, PTA for type, and feet and leg composite index were similar, with two families significant for these traits ($P_c < 0.005$). Marker BMS2361 on BTA20 was associated with differences in protein percentage. This result seems to be built on strong support from one family ($P_c = 0.001$) and moderate support from two other families ($P_c < 0.05$). It is possible that this QTL is the same as that reported on BTA20 by Zhang et al. (1998) and confirmed by Arranz et al. (1998) affecting protein percentage.

Two newly significant associations were identified for markers that were analyzed in our previous report (Van Tassell et al., 2000). These new associations may have been detected because the predicted breeding values were updated with more accurate values as phenotypic data collection has continued. Marker BM43 on BTA5 was associated with changes in canonical conformation trait 4 in family 5, at $P_c = 0.0001$, on a within-family basis. The same marker was associated with changes in dairy form at $P_c = 0.0006$ in the across-family analysis, in which four families provided moderate support ($P_c < 0.05$). A similar QTL affecting many size and udder traits including chest width, body capacity, udder depth and dairy character, was reported by Schrooten et al. (2000). The markers in the two studies are approximately 18 cM apart and may be detecting the same QTL. Marker BMS1385 on BTA27 was associated with changes in dairy form in the across-family analysis. This result is probably due to strong support from family 2 ($P_c < 0.0001$) as indicated above and moderate support from one other family ($P_c < 0.05$).

If the number of significant tests expected under the null hypothesis is compared with the number observed, substantial evidence exists for QTL affecting several traits in this population. A total of 41,030 trait-marker-family combinations was tested in this study, resulting in 41 significant tests expected for the within-family analysis by using 0.001 comparisonwise significance thresholds and 126 were actually observed. For a significance threshold of 0.01, a total of 788 significant tests were observed and 410 were expected by chance. Similarly, for across-family analyses, a total of 9027 trait-marker combinations were present. With this many tests, 9 and 90 significant tests were expected by chance for the across-family analysis, with significance levels of 0.001 and 0.01, respectively. A total of 50 and 231 significant results were observed at these levels. Finally, a total of 56 traits (ordinary and canonical) were analyzed, resulting in six expected significant tests with the empirical traitwise P values of 0.1 for within- and across-family analyses, and 30 and 33 were observed. Note that results for PTA that were redundant with DD results were not included in Tables 2 and 3 but are included in these counts.

Of the 39 marker and trait combinations we previously identified (Van Tassell et al., 2000), 10 of these effects are no longer significant at the traitwise level. This is not surprising for the following two reasons: First, results from the latest 50 markers increased the total number of statistical tests used in the analysis by 60%; second, the 10 marker-trait combinations were not highly significant, with P_e between 0.1 and 0.05. Those associations that remain significant at the traitwise level had $P_e < 0.05$. One exception was detected for marker BMS2519 on BTA2 for PTA productive life in family 8, with $P_e = 0.009$. In the current analysis, $P_e = 0.47$; however, this difference is most likely due to a change in the way that the productive life trait is now calculated (see http://aipl.arsusda.gov/memos/html/multiplrevised.html).

To date, several studies have reported QTL affecting milk production traits (Arranz et al., 1998; Ashwell et al., 1998a, 1998b; Ashwell and Van Tassell, 1999a; Georges et al., 1995; Heyen et al., 1999; Riquet et al., 1999; Spelman et al., 1996; Zhang et al., 1998) and one study showed QTL affecting conformation traits (Schrooten et al., 2000). Although different families, markers, analysis methods, and significance thresholds were used in these studies, several QTL affecting milk traits have been detected and confirmed in more than one of these studies. Because only two studies have attempted to identify QTL associated with conformation traits and because those traits are defined differently in the two countries, it is not surprising that discrepancies exist between results reported by Schrooten et al. (2000) and results from our study.

These results provide additional evidence that the granddaughter design can be used to detect QTL affecting economically important traits in commercial dairy cattle populations. However, before these QTL can be used by the AI industry, markers closely flanking the QTL must be identified and descendants of

these families must be evaluated to determine the usefulness of these QTL in a marker-assisted selection program. Now that this genome scan is complete, efforts will be focused on studying a population of contemporary animals (Ashwell and Van Tassell, 1999b) in regions where we have detected putative QTL.

CONCLUSIONS

This study has identified associations between MS markers and QTL for milk production, SCS, and conformation traits in eight Holstein grandsire families by using genotypic data from 155 markers located throughout the genome. These results indicate that 1) BTA7 may contain a QTL affecting SCS; 2) BTA4, 14, 16, and 20 may contain QTL affecting udder traits; 3) BTA12 and 23 may contain QTL affecting feet and leg traits; 4) BTA4, 5, 9, 18, 22, and 27 may contain QTL affecting body conformation; 5) BTA3, 6, 14, 18, 20, and 28 may contain QTL affecting protein percentage; and 6) BTA14 may contain QTL affecting fat yield and fat percentage. These results provide additional support for highly significant QTL identified by other research groups but also identify other QTL not detected in these other studies. These findings should help researchers identify the most useful markers available for QTL detection and, eventually, for marker-assisted selection for improvement of these economically important traits.

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