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Anchoring of bovine Chromosomes 4, 6, 7, 10, and 14 linkage group telomeric ends via FISH analysis of lambda clones

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Abstract. We report the placement of 34 new microsatellite (ms) markers, isolated from a lambda phage genomic clone library, on the bovine genetic map by linkage to published markers. Five of these markers lie at or near the ends of linkage groups and are used to establish chromosomal coverage and orientation. Fluorescence in situ hybridization (FISH) analysis demonstrates that the linkage groups on the U.S. Meat Animal Research Center (MARC) map extend to the telomeric region of Chromosomes (Chrs) 7 and 10. Linkage groups on Chrs 4, 6, and 14 appear to be less inclusive.

Introduction

Genetic maps of livestock genomes have recently been constructed to aid in the localization and/or identification of loci affecting traits of economic significance (ETL). The usefulness of the genetic map in identifying ETL is a function of the overall coverage of the genome and the integration of the genetic linkage map with the cytogenetic (physical) map. A major goal of map construction has thus been the generation of polymorphic markers physically localized to regular intervals along the chromosome and at the extremes of the linkage groups, to use for scanning the genome of populations segregating phenotypes of interest (Fries 1993; Solinas-Toldo et al. 1993; Beattie 1994; Ellegren et al. 1994; Ferretti et al. 1994; Smith et al. 1995; Hawkins et al. 1995; Mezzelani et al. 1995).

The primary source of markers on the current bovine map is the abundant, widely dispersed, and highly polymorphic Type II (O'Brien et al. 1993) class of markers, mainly simple dinucleotide (ms) repeats (Bishop et al. 1994; Barendese et al. 1993, 1994; Stone et al. 1995). The difficulty of physical localization of the small inserts typically used to identify and sequence ms (Bishop et al. 1994; Barendese et al. 1994; Stone et al. 1995) has limited the number of linked, highly polymorphic markers that have been physically assigned in the bovine genome by in situ techniques (Mezzelani et al. 1995; reviewed in Eggen and Fries, 1995). This lack of anchors makes genome coverage estimates of the genetic linkage map difficult. We therefore screened a bovine genomic library in lambda vector (average insert size 16 kb) and identified 34 polymorphic ms markers for use in integrating the physical and genetic linkage maps of cattle. Markers that map at or near the terminus of a linkage group, or at a previously unanchored region of the genome, were physically mapped by FISH analysis to establish the extent of that group. This analysis has provided six new physical assignments of linked markers to the bovine genome that establish the coverage of five linkage groups at their telomeric ends.

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Materials and methods

Marker isolation. Lambda phage from a commercial genomic library (Lambda Dash II vector, Stratagene, average insert size 16 kb) were plated according to the manufacturer's instructions at a density of 100–500 pfu/150-mm plate. Plaque lifts, hybridizations, and secondary screenings with $(CA)_{11}$ or $(GT)_{11}$ probes were performed essentially as described (Stone et al. 1995). Positive secondary plaques were picked and plated at high density on 100-mm plates, and plate lysate DNA preps prepared by column chromatography (Quiagen, Chatsworth, CA) as per the manufacturer's protocol, digested with restriction enzyme, subcloned, and sequenced as described (Alexander et al. 1996). Microsatellite flanking sequences were analyzed for repetitive element content and repeat length, and primers developed as described (Stone et al. 1995).

Linkage analysis. Markers were initially genotyped across the 28 parents of the MARC mapping population, and subsequently across offspring having at least one heterozygous parent as described (Bishop et al. 1994). The genotypic data were entered into the MARC database (Keele et al. 1994) to calculate two-point linkages with previously mapped markers by use of the TWOPOINT option of the CRIMAP program (Green et al. 1990).

FISH analysis. Lambda DNA was labeled with biotinylated nucleotide by nick translation (Gibco BRL, Grand Island, NY), hybridized to R-banded metaphase spreads of bovine chromosomes as per the manufacturer's protocol (Oncor, Gaithersburg, MD) as described (Lichter et al. 1990; Ponce de León et al. 1996), and photographed with a cooled camera with digital enchancement (CCD) camera.

Results

We identified ms-containing lambda phage genomic clones by hybridization as described (Rohrer et al. 1994; Stone et al. 1995). The ms were subcloned into plasmid or m13 vectors, and 250 individual positive clones were sequenced, yielding 104 sequences suitable for primer pair development. The markers were evaluated for their ability to amplify genomic DNA and for polymorphism within the MARC mapping population (Bishop et al. 1994). Polymorphic, scorable markers (34/104) were genotyped across families having at least one heterozygous parent. The average number of informative meioses per marker for the lambda-derived markers was 225 (range 24–332). Marker designations, primer sequences, PCR conditions, and total number of informative meioses for each of the 34 markers are shown in Table 1.

All 34 markers showed linkage with at least one mapped marker at a LOD score greater than 5, and all but one (BL1024) showed linkage of LOD > 3 to multiple markers (average of 6.4 linked markers per lambda-derived marker, range 1–14). Table 1 indicates the marker designation from Bishop and associates (1994) that had the highest LOD linkage to each lambda-derived marker, with the LOD score and recombination fraction. The chro-

Table 1. Mapping data of lambda phage-derived microsatellite markers. Sequence of primers and temperature of annealing step for each marker is shown, with minimum and maximum allele sizes and total number of distinguishable alleles. The LOD score and recombination fractions for linkage with the indicated published marker are shown, resulting from linkage calculation based on the number of informative meioses indicated. The FISH column indicates the physical assignments for those markers subjected to in situ hybridization.

Locus	Chr	Forward primer sequence	Reverse primer sequence	Annealing Temp (°C)	No. Informative meioses	Allele sizes (bp) Min	Max	N[a]	Linked marker[b]	LOD	Recomb. fraction	Physical Assignment (FISH)
BL26_1	1	TGTAAGCCACCCCTATTCCC	CTTCTTGGAGGAGGCACG	56	244	154	138	7	*BM864*	37.3	0.10	
BL1001	2	AGACGAGGCAACTTGGAATCT	CGTGTCAGAAAACATAACTGCC	58	119	171	152	6	*OarFCB20*	29.0	0.02	
BL1028	2	GCTTTCCCTCTCATCCTGG	GAACTGTGTGGCAGAGGTTG	56	238	115	105	6	*BM2113*	33.1	0.03	
BL1048	3	ACCGCCACAAGGGAAATC	AAGGCAACAGCATATGAAACTG	58	124	119	101	4	*INRA003*	12.5	0.13	
BL1024	4	CACTCGGAATTCTCCAGAGC	TTGATGTCTCAGTCAATCTCCC	58	313	110	96	7	*RM188*	18.4	0.21	
BL1030	4	TTGATGGATGAATGGGTAAAG	ATCTTGCTTCCATACCATGC	58	261	166	146	8	*RM188*	14.5	0.22	
BL1121	4[c]	CCAGGCTAGGAAGGCAGTAG	AGGGTACAAAAATCCCACACC	58	200	100	88	4[d]	*RM088*	32.6	0.04	4q33–35
BL4	5	AAATTTTTCATCCTTCTTTCTGAC	TCACCCTGACTGTGAATGC	56	271	163	145	7	*RM500*	33.5	0.06	
BL32_1	6	GGAGAATTTACCAGGCTCAGG	GAATTTGATGTCCTCTTCATGG	56	274	144	140	2	*BP7*	10.5	0.14	
BL1038	6[c]	GGCAAGCTAGAGTCAGACACG	GCAAAAGTCTAGGTGAAATGCC	60	240	109	97	5	*BM2320*	39.3	0.02	6q35
BL1099	6	AGAAAAGGAGGGGGAAATATG	GACATTCTGATGGGAAGCTAAC	58	118	211	191	10[d]	*BM4621*	11.38	0.07	
BL5-1	7	CATGGACAGAGAAGTCTGGTAGG	ACCATCATTTAACCCATATCAACC	56	270	162	136	14[d]	*BP41*	29.7	0.03	
BL1043	7[c]	AGTGCCAAAAGGAAGCGC	GACTTGACCGTTCCACCTG	58	332	123	99	10	*ILSTS006*	21.1	0.19	7qter
BL1067	7	AGCCAGTTTCTTCAAATCAACC	ATGGTTCCGCAGAGAAACAG	58	280	106	90	5	*BP41*	28.0	0.02	
BL36-2	8	CAGGAAGAAATATACGGCACG	TCATTATCTCCAGTCACCATGC	54	270	160	140	7[d]	*BM4006*	23.0	0.03	
BL1080	8	TTCTGAATGCACCCTTGTTTAG	CTGGGCAACTAACTAATCCTGG	58	269	143	119	7	*BM4006*	23.9	0.06	
BL1035	10	ACAGCCTCCCTCACCAAAC	GTCTGACTGCAAATGTGAGACC	58	281	111	79	11	*BRRIBO*	46.6	0.05	
BL1134	10[c]	ACACTCGCAAGGAAGACCC	TTCCCCCAGCTTTAGTTTACC	58	166	125	111	6	*OarAE64*	10.0	0.05	10qter
BL1103	11	ATGTCCCCATCCAAAATCAC	AAGCATCTTCCACCTGTTTAGC	58	250	126	102	10	*BM746*	31.0	0.02	
BL1022	12	CAAAGCAATTTAAAAGCTGCC	AAGGGAGAGGACTGGTTTCTG	58	209	114	98	5	*BM6116*	26.6	0.05	
BL1071	13	AGAAGGACAGAGACCACAGGC	TTGAGGTGAAGAGGTCCACC	58	319	200	178	9	*AGLA232*	35.6	0.12	
BL1036	14[c]	TAGCTTATGCCATTGTTTTTGC	ATCTGATGTGGGTTTCTGACTG	56	231	200	178	8	*BM6425*	24.9	0.12	14q23–24
BL1029	14	CAAATCAGCCTCTCCTCTTCC	GTGCTTCCAGAGACAATAAAGG	58	281	168	142	6	*BM302*	22.5	0.07	
BL1009	14	TCTGTGTCAAAGTCCTGAGGG	CCTGGCATTCTGCAGTCC	58	275	177	157	8[d]	*ILSTS008*	35.1	0.05	
BL1095	15[c]	TCCCTCTACCATATATTTCCCC	CATTAGCATGGAAAAACCTCTG	58	286	176	164	6	*BM848*	40.1	0.04	
BL1016	18	GCACTGCCCTGAACGCTAC	CAAAGCAATATGCTGTTTGGATG	58	192	110	106	4[d]	*BM7109*	11.7	0.21	
BL1006	19	CCGATACAGGTCCAAAAGGC	TCATGCGACTTGAACAGCTC	56	201	145	101	8[d]	*MAP2C*	32.7	0.06	
BL6-1	24	TTTTTCACTGTACTAAAACGCTGC	TCTCAAGTTTACATTTCCCTTTCC TCTCAAGTTTACATTTTCCTTTCC	54	123	163	149	5	*BM226*	11.6	0.09	
BL1100	25	ACATGGAGCAGAGGCAGC	AGTACAAGCAGGGGTGCG	58	313	87	71	6	*BMC3224*	36.7	0.07	
BL1040	26	CCCTCGCAAGCAAAGAAAG	GCATTGTTGTTTCTTTACAGGC	58	314	101	87	5	*BM1314*	44.2	0.03	
BL22	X	CTGCTCCCCTGACTGCCC	TTTCTTCCTTTATCTGTTCAGTTGG	64	49	198	188	5[d]	*TGLA325*	12.0	0.00	
BL1045	X	TGCCAGAACAAGTCACAAGC	CTCCAAGGGTGTCTCTATCCC	58	24	94	90	3[d]	*BM2713*	7.2	0.00	
BL1031	X	CAAAGAGCTGGACACAACTG	TTGGCTCTTGCCTTTCTAGG	58	38	125	113	5[d]	*BM4604*	5.4	0.00	
BL1098	X[c]	CCACAACTTCCAGAAGCCTC	CAGAAACCACCCAAACTAACC	58	295	223	205	7[d]	*BM2713*	35.8	0.00	Xp14

[a] Number of distinguishable alleles observed in the MARC population.
[b] Previously published marker with the highest LOD score two-point linkage.
[c] Marker at or near the extremes of the linkage group.
[d] Includes a null allele.

mosome column of Table 1 indicates that lambda-derived markers fall on 16 of the 29 autosomes and on the X Chr. Marker distribution roughly parallels the relative size of the chromosomes, with the larger chromosomes (#1–14, X) having greater probability of harboring multiple markers, consistent with a random distribution of ms throughout the genome.

Markers were ordered with respect to published markers with the ALL, BUILD, and FLIPS options of the CRIMAP version 2.4 program (Green et al. 1990). The calculated position of each marker in its respective linkage group will be published in an update of the bovine linkage map (S. Kappes et al. in press). The analysis indicated that five of the markers lie at or near (<15 cM) the extremes of their respective linkage groups (marked by asterisk in chromosome column of Table 1). These markers were chosen for cytogenetic analysis to allow accurate estimation of linkage group coverage.

Two-point linkage and physical mapping data for the six chromosomes subjected to cytogenetic analysis are summarized in Table 1 and Fig. 1. Marker *BL1134* lies 4 cM distal of marker *OarAE64* (Table 1), making it the terminal marker of the Chr 10 linkage group (Bishop et al. 1994; S. Kappes unpublished data). FISH analysis demonstrates that *BL1134* lies at the telomere of the chromosome at 10q3.6 (Fig 2a). Thus, the linkage group extends to the telomeric end of bovine Chr 10. Similarly, marker *BL1043* is the terminal marker of the Chr 7 linkage group, lying 19 cM distal of marker *ILSTS006*, and also appears telomeric at 7q2.8 (Bishop et al. 1994). Marker *BL1121* lies 5 cM proximal from the terminal marker (*AGLA227*) of the Chr 4 linkage group (Bishop et al. 1994) and is localized to 4q3.3–3.5 (Fig. 2b). Marker *BL1038* is the terminal marker of the Chr 6 linkage group, lying 2 cM distal of marker *BM2320*, and is localized near, but not at, the telomere at 6q3.5 (Fig. 2c). Marker *BL1036* lies 13 cM proximal to *BM6425*, the terminal marker of the Chr 14 linkage group, and is localized proximal from the telomere at 14q2.3–2.4. Finally, *BL1098* was mapped to the X Chr, albeit near the middle of the linkage group, and was assigned to Xp1.4 (Fig 2d).

Discussion

The bovine linkage map has developed very rapidly, expanding from a handful of linked markers to over 1000 in the last few years (Barendese et al. 1994; Bishop et al. 1994; Stone et al. 1995) As part of an effort to improve the integration of the physical and genetic linkage maps, we have screened a lambda genomic library to produce 34 random, polymorphic ms markers suitable for physical assignment.

Cytogenetic analysis of marker *BL1043* demonstrates that the linkage group extends to the telomere of Chr 7 (Fig 2e). The assignment of this marker allows estimation of linkage group coverage when combined with the assignment of marker *BL5* to 7q1.4 (Grosz et al. in press; see Fig. 1). Since recombination rate near centromeres has been observed to be relatively low for many mammalian chromosomes, the 20 cM flanked by markers proximal to

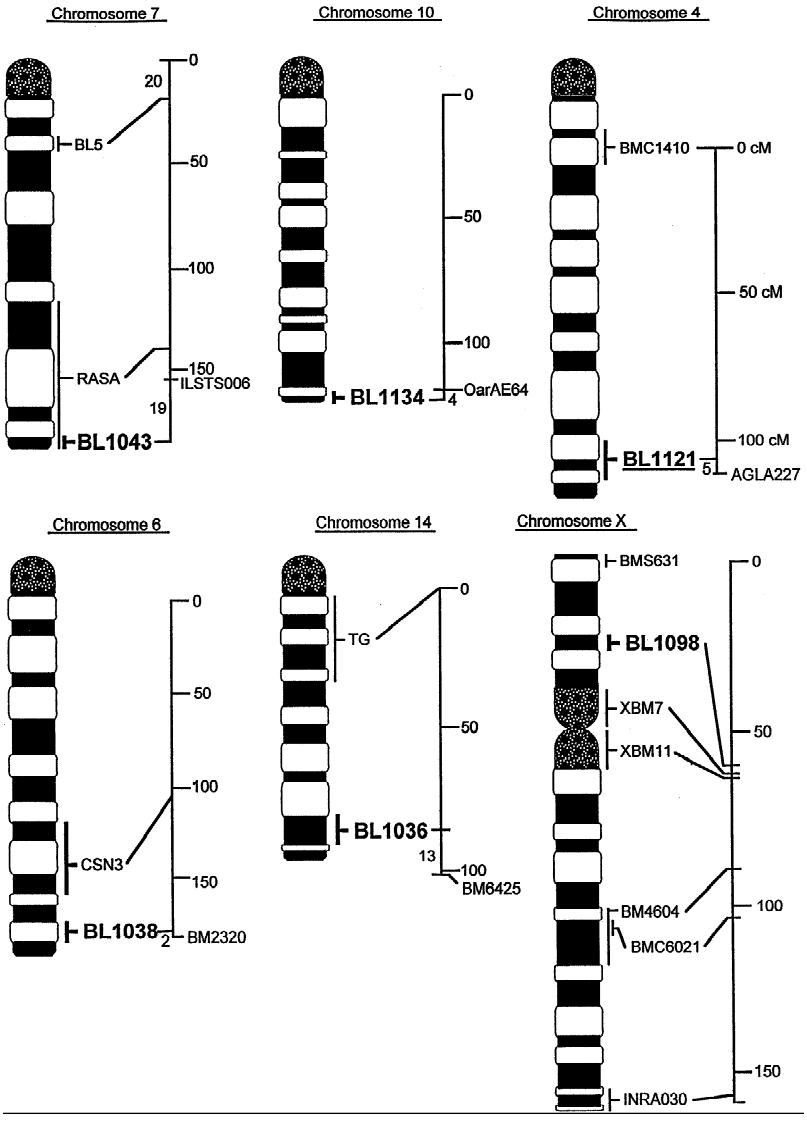

Fig. 1. Physical assignments of linked markers on the MARC genetic linkage map. Standard R-banded karyotypes of the indicated bovine chromosomes are shown, with the assignments of lambda-derived markers described in this manuscript shown in bold type. To the right of each chromosome karyotype is an ideogram of the current linkage group with the positions of markers described in the text shown along a genetic distance scale (in centimorgans).

BL5 is likely to greatly expand the physical coverage such that the linkage group probably approaches the centromere. Previous assignment of RAS p21 protein activator (RASA), which appears on the linkage map 34 cM proximal of *BL1043*, orients the linkage group but is less precise (7q2.4–2.8; Fig. 1; Eggen et al. 1992). Therefore, the assignment of *BL1043* establishes that the MARC Chr 7 linkage group encompasses the majority of the chromosome, from 7qter to a point near the centromere.

Assignments reported for Chr 10 include the genes for Hsp 70-3 and cytokeratin 8-like 1, as well as DNA segment GMBT19

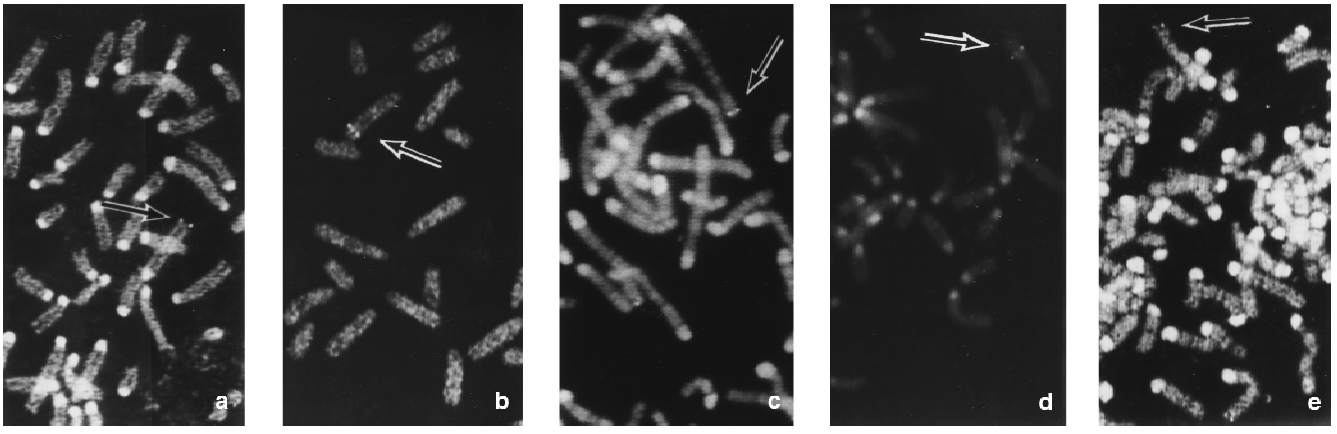

Fig. 2. Representative FISH partial metaphase spreads with bovine genomic lambda phage clone probes. Markers used were: (a) *BL1134,* (b) *BL1121,* (c) *BL1038,* (d) *BL1098,* (e) *BL1043.*

(summarized in Eggen and Fries 1995), but none of these loci appear on the linkage map. Therefore, while the assignment of *BL1134* to 10qter demonstrates that the MARC linkage group extends to the telomere, overall coverage of the chromosome cannot be determined until markers from the centromeric end of the linkage groups are physically localized. Directed, iterative screening of cosmid libraries (Smith et al. 1995) to obtain large clones containing these markers has been undertaken to establish overall coverage (Lopez et al. in preparation).

The other four physical assignments in this manuscript demonstrate that the coverage of the MARC bovine linkage map remains incomplete (summarized in Fig. 1). For example, *BMC1410* has been assigned to 4q1.3–1.4 (Hawkins et al. 1995) and is the centromeric end of the Chr 4 linkage group. Thus, the assignment of *BL1121* to 4q3.3–3.5 indicates that the linkage group, currently 111 cM in length and containing 44 markers, does not cover Chr 4 in the region 4q1.1–1.2 and 4q3.6. An rRNA sequence cluster has been assigned to 4qter and the gene for inhibin beta A to 4q2.6 (Neibergs et al. 1993; Eggen and Fries 1995), but neither locus appears on the linkage map.

The assignment of *BL1038* to 6q3.5 indicates that the MARC map of Chr 6 does not include markers in the vicinity of 6q3.6. The overall coverage cannot be estimated accurately in the absence of a linked marker physically assigned at the centromeric end. However, a microsatellite derived from a cosmid clone assigned to 6q12–14 (Kühn et al., 1996) is now available and will allow the estimation of overall coverage of Chr 6 if it is found to be polymorphic in the mapping herd.

On Chr 14, the relatively broad physical assignment of thyroglobulin (*TG*) and marker *GMBT6* to 14q1.2–1.6 and 14q1.1–1.6, respectively, has established orientation of the linkage group (Threadgill et al. 1990; Georges et al. 1991). *TG* lies 3 cM closer to the centromere than *ILSTS011* (Daskalchuk and Smutz, in press), the terminal marker in the published MARC linkage group (Bishop et al. 1994), and 10 cM distal from the terminal marker of the current linkage group. Thus, the assignment of *BL1036* to 14q23–24 indicates that the 102-cM current linkage group covers approximately 50–90% of the chromosome, depending largely on the actual position of *TG* (Fig. 1).

ll of the above data are consistent with an estimate that the current MARC linkage map represents approximately 95% coverage of the bovine genome. The MARC map currently includes 1260 markers, the bulk being ms isolated by random screening of clone libraries from genome-wide cloning approaches. As such, it contains the largest number of linked markers of any other published linkage map by a factor of 2 or more (Fries et al. 1993; Bishop et al. 1994; Barendse et al. 1994; Eggen and Fries 1995), suggesting that it represents the most extensive coverage of the bovine genome. Given the limited resources available to the livestock mapping community, the random approach to marker isolation is no longer an efficient means to increase coverage, since the majority of randomly isolated markers will fall within the region already covered. A more efficient method of expanding coverage is through the use of microdissected chromosome libraries specific to areas currently lacking markers. Physically assigned, cytogenetic anchors such as the ones described in this manuscript provide an important guide for the microdissection to these regions. In combination with a concerted effort to isolate anchors at all linkage group ends by directed, iterative screening of cosmid libraries (Lopez et al., in preparation), the data presented here provide the physical framework for more efficient expansion of the linkage map coverage of the bovine genome.

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