



RESEARCH

# A Second-Generation Linkage Map of the Bovine Genome

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We report a bovine linkage map constructed with 1236 polymorphic DNA markers and 14 erythrocyte antigens and serum proteins. The 2990-cM map consists of a sex-specific, X chromosome linkage group and 29 sex-averaged, autosomal linkage groups with an average interval size of 2.5 cM. The map contains 627 new markers and 623 previously linked markers, providing a basis for integrating the four published bovine maps. Orientation and chromosomal assignment of all the linkage groups, except BTA20 and BTA22, was provided by 88 markers that were assigned previously to chromosomes. This map provides sufficient marker density for genomic scans of populations segregating quantitative trait loci (QTL) and subsequent implementation of marker-assisted selection (MAS) mating schemes.

[Linkage groups for all 29 autosomes and the X and Y chromosomes are presented at <http://www.cshl.org/gr/>.]

Livestock genetic linkage maps are developed for identifying regions of the genome that influence economically important traits. Most traits of interest in cattle are quantitative in nature and relate to production efficiency, reproduction, or carcass characteristics. The continuous phenotypic distribution observed in most quantitative traits reflects the joint action of multiple loci and environmental influences that increase the difficulty in identifying genetically superior animals. Identification of quantitative trait loci (QTL) can improve selection accuracy and intensity.

Linkage maps with low marker density have been published for cattle (Barendse et al. 1994; Bishop et al. 1994; Georges et al. 1995; Ma et al. 1996b), swine (Ellegren et al. 1994; Rohrer et al. 1994; Archibald et al. 1995), sheep (Crawford et al. 1995), and goats (Vaiman et al. 1996). Average marker interval exceeds 5 cM in pigs and 10 cM in cattle, sheep, and goats. These maps have been used to identify loci in cattle [horn development (Georges et al. 1993a), weaver disease (Georges et al. 1993b), milk production (Georges et al. 1995), roan

coat color (Charlier et al. 1996), muscle hypertrophy (Charlier et al. 1995)]; sheep [fecundity (Montgomery et al. 1994) and muscle hypertrophy (Cockett et al. 1994)]; and pigs [fat and growth traits (Andersson et al. 1994) and disease resistance (Edfors-Lilja et al. 1995)]. Most of these loci have been mapped to >10-cM intervals or they extend beyond the end of the linkage group. Although marker density is sufficient for detecting most QTL, the current maps lack the resolution required for efficient use of marker-assisted selection (MAS) or fine mapping and positional cloning. A second generation map consisting of 1042 loci and an average interval size of 2.23 cM (Rohrer et al. 1996) improves this situation for pigs, but the average interval of the highest resolution cattle map (Bishop et al. 1994) still exceeds 10 cM.

We report a high resolution (average interval 2.5 cM) bovine linkage map with 1250 polymorphic loci covering 2990 cM. Six hundred twenty-three previously linked markers provide a basis for integrating the four published bovine maps (Barendse et al. 1994; Bishop et al. 1994; Georges et al. 1995; Ma et al. 1996b). This map increases the power of detecting QTL and improves the potential resolution of a mapped QTL provided sufficient number of re-

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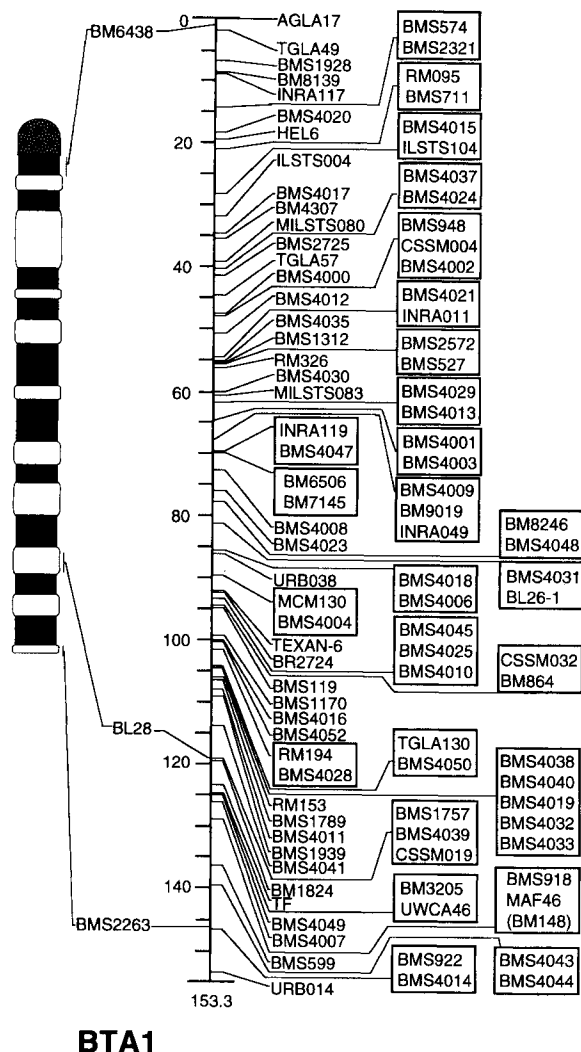
E-MAIL [kappes@map.marc.usda.gov](mailto:kappes@map.marc.usda.gov); FAX (402) 762-4390.

combinant meioses are available. In addition, this map will augment QTL detection and MAS in sheep and goats because a common set of bovine and ovine markers are found on the ovine, caprine, and current bovine linkage maps (Crawford et al. 1995; Vaiman et al. 1996; M.G. de Gortari, B.A. Freking, A.M. Crawford, S.M. Kappes, R.T. Stone, and C.W. Beattie, in prep.), and marker order is virtually identical between sheep and cattle (S.M. Kappes, M.G. Gortari, B.A. Freking, A.M. Crawford, R.T. Stone, J.W. Keele, K. Dodds, and C.W. Beattie, unpubl.; M.G. de Gortari, B.A. Freking, A.M. Crawford, S.M. Kappes, R.T. Stone, and C.W. Beattie, in prep.).

## RESULTS

A second-generation bovine linkage map was constructed with 1250 loci in 29 sex-averaged, autosomal linkage groups and one female-specific (BTAX) linkage group. The male-specific linkage group (BTAY) includes the pseudoautosomal region and two (BM861 and INRA189) Y chromosome-specific markers. The BTA1 linkage group is presented in Figure 1, and all linkage groups are presented at the *Genome Research* Web site (<http://www.cshl.org/gr/>). Each linkage group is aligned next to the R-banded karyotype (ISCNDA 1990) of its respective chromosomes. All linkage groups, except for BTA20 and BTA22, are anchored and oriented to the chromosome with 88 physically assigned, polymorphic markers. The orientation of the BTA17 linkage group is supported by physical assignment of the  $\gamma$ -fibrinogen (FGG) gene on the Barendse et al. (1994) map. References for each physical assignment are presented in Table 1. The BTA20 linkage group is indirectly anchored by the previous assignment of AGLA29 (Georges and Massey 1992) to synteny group U20b. The MAP1B (referenced in Barendse et al. 1994) gene was used to assign U20b to BTA20. The BTA22 linkage group is also indirectly anchored by the previous assignment of INRA026 (Vaiman et al. 1994a), CSSM006 (Moore et al. 1994) and HUJ175 (Shalom et al. 1994) to synteny group U12. The lactoferrin gene was used to assign U12 to BTA22 (Schwerin et al. 1994). The physical assignment and linkage group nomenclature for BTA25 and BTA29 (Barendse et al. 1994; Bishop et al. 1994; Ma et al. 1996b) have been interchanged according to the recommendation of Popescu et al. (1996) to eliminate the inconsistency identified between linkage group nomenclature and the traditional (1:29) Robertsonian translocation (Eggen et al. 1994; Schmutz et al. 1996).

Clone and primer sequences of all available



**Figure 1** Linkage group for bovine chromosome one. The linkage group is oriented next to the R-banded karyotype (ISCNDA 1990) of the chromosome and labeled below for *Bos taurus* (BTA). Linkage groups for all 29 autosomes and the X and Y chromosomes are presented at the *Genome Research* web site (<http://www.cshl.org/gr/>). BTA1 is shown here. Markers with physical assignments are at left; their assignments (Table 1) are represented on the R-banded chromosome. Markers in parenthesis (see Web site) are a second set of primers for the same microsatellite as the marker above. No recombination events were detected between markers within a box; therefore, the order in which they are presented is arbitrary. In general, marker order in intervals <5 cM should be considered tentative as their statistical support was often less than a lod score of 3.0.

markers were compared to identify duplicate markers for the same microsatellite. Seventeen markers (markers in parenthesis in Fig. 1 on Web site) were identified as duplicates, consistent with the pre-

dicted number of duplications reported by Stone et al. (1995). Occasionally, a set of primer pairs amplified more than one polymorphic locus. The primer pair for BMS4049 amplified a BTA1 (BMS4049) and BTA6 (BMSB4049) locus, and primers for BM9248 amplified a BTA13 (BM9248), BTA12 (BMA9248), and BTA2 (BMB9248) locus. Only six (6/1256, 0.5%) unlinked markers (10–89 informative meioses) exist in the data set, including the erythrocyte antigen EAJ. No significant twopoint linkages were detected for EAJ (21 informative meioses), although Ma et al. (1996b) reported the linkage of EAJ to the end of their chromosome 11 linkage group. When the lod score criteria was relaxed to 2.0, a two-point linkage was detected between EAJ and HEL13 ( $\theta = 0.08$ ;  $Z = 2.08$ ), consistent with Ma et al. (1996b). Fifty-five of the linked markers, including erythrocyte antigens and serum proteins, are associated with genes (Table 2). References for each marker are summarized in Table 3 and on the World Wide Web at <http://sol.marc.usda.gov/>.

Linkage group length and marker density are summarized in Table 4. The longest (BTA1, 153.3 cM; BTAX, 150.5 cM) and shortest (BTA28, 52.4 cM) linkage groups were anchored to the longest and shortest chromosomes, respectively, as reported by Popescu et al. (1996). Linkage groups for larger chromosomes (BTA1-10 and X) tended to be shorter than the predicted length, whereas linkage groups for the smaller chromosomes (BTA15–BTA29) are longer than expected, assuming equal coverage of all chromosomes. The tendency of lower recombination rates on longer chromosomes compared to shorter chromosomes is consistent with recombination rates of yeast chromosomes of different lengths (Kaback et al. 1992), long and short chromosome arms in humans (Morton 1991), and porcine chromosomes (Rohrer et al. 1996).

The number of loci per linkage group was evaluated to determine whether microsatellites are randomly distributed across the bovine genome. BTA1, BTA6, BTA23, BTA25, and X linkage groups contain nonrandomly generated microsatellite markers from BTA1-, BTAX<sub>p</sub>-, and BTAX<sub>q</sub>-specific libraries (Ponce de León et al. 1996; Sonstegard et al. 1997a,b) that were excluded from the evaluation. The observed number of loci per linkage group was compared to the expected number, as determined by simulation (100,000 replications) using estimates of chromosome length reported by Popescu et al. (1996). Loci number per linkage group was between the 2.5 and 97.5 percentile for all of the linkage groups except BTA11 and BTAX. The number of loci for BTA11 (68) was eight loci above the 97.5% level,

and BTX (48) was one locus below the 2.5% level. Deviation from the expected number of loci could have been caused by nonrandom selection of published markers during later stages of map development. Published markers were selectively added to the map if they were linked to marker-deficient regions or had been assigned physically. The lower number of loci on the BTAX linkage group was expected, as some markers were developed from male genomic libraries.

Marker heterozygosity was determined with all (polymorphic and monomorphic) microsatellite markers genotyped on the parents of the USDA Meat Animal Research Center (MARC) reference population (Bishop et al. 1994). The number of microsatellites genotyped per parent ranged from 1372 to 1423 markers. Average marker heterozygosity was 40.2, 42.5, 59.0, and 76.0% for linebred *Bos taurus* ( $n = 1$ ), purebred *B. taurus* ( $n = 13$ ),  $F_1$  *B. taurus* ( $n = 10$ ), and  $F_1$  *Bos indicus/B. taurus* ( $n = 4$ ) parents, respectively. Linked autosomal markers averaged 223 informative meioses from a potential of 412 informative meioses, whereas X-linked markers averaged 85 female informative meioses from a potential of 203 female informative meioses.

A relative scale (1–5) indicating “ease of scoring,” was implemented for the last 802 markers genotyped to identify markers suitable for genomic scans in QTL studies. This score is accessible via the World Wide Web at <http://sol.marc.usda.gov/>. Eighty-five percent (683) and 7% (59) were classified as primary (score 1 and 2) and secondary (score 3) markers, respectively. The remaining 7% are difficult to score (score 4 and 5) and should only be used when both parents can be genotyped with progeny or to identify large genomic clones that contain additional polymorphisms that are easier to score.

Although two detected recombination events within a small interval (<20 cM) generally indicate genotyping errors, some double recombination events are real. Double recombination events were considered actual occurrences after the genotypes causing the double crossovers were validated with a second PCR reaction. Some double recombination events are also documented by more than one marker genotype supporting each crossover event. The number of detected double crossovers within 20-cM intervals per chromosome (Table 4) is dependent on the number of markers and the marker density of the chromosome. Although the linkage groups for BTA2 and BTA11 are similar in length (120 and 129 cM) and marker density (1.9 average interval size), 8 and 60 double crossovers were detected in the two linkage groups. The higher num-

**Table 1. References for Linked Markers with Physical Assignments**

Marker	Physical location	Reference
BM6438	1q1.2	Sonstegard et al. (1997b)
BL28	1q4.2	Grosz et al. (1997)
BMS2263	1q4.6	Sonstegard et al. (1997b)
IDVGA-64	2q4.4	Mezzelani et al. (1995)
IDVGA-37	2q4.5	Mezzelani et al. (1995)
IDVGA-2	2q4.5	Mezzelani et al. (1995)
BL41	3q2.1	Grosz et al. (1997)
IDVGA-53	3q2.1	Mezzelani et al. (1995)
IDVGA-35	3q3.5	Mezzelani et al. (1995)
IDVGA-27	3q3.7	Mezzelani et al. (1995)
BMC1410	4q1.3-1.4	Solinas-Toldo et al. (1995)
IDVGA-51	4q3.1(6q3.1) <sup>a</sup>	Mezzelani et al. (1995)
BL1121	4q3.2-3.3	Smith et al. (1997)
BL37	5q2.2	Grosz et al. (1997)
BMC1009	5q2.3	Hawkins et al. (1995)
ETH 10	5q2.5	Solinas-Toldo et al. (1993)
ETH 2	5q3.5	Solinas-Toldo et al. (1993)
IDVGA-9	5q3.5	Mezzelani et al. (1995)
CSN3, CSN1S1	6q2.6-3.3	Threadgill and Womack (1990); Solinas-Toldo et al. (1995)
ETH8	6q3.5	Solinas-Toldo et al. (1993)
BL1038	6q3.5-3.6	Smith et al. (1997)
BL5	7q1.4	Grosz et al. (1997)
IL4	7q1.5-2.1	Buitkamp et al. (1995)
RASA	7q2.4-qter	Eggen et al. (1992b)
BL1043	7q28	Smith et al. (1997)
IDVGA-11	8q1.4	Mezzelani et al. (1995)
IDVGA-52	8q2.3	Mezzelani et al. (1995)
CSSM025	9q1.7-1.9	Johnson et al. (1995)
BMC701	9q2.2	Hawkins et al. (1995)
INRA144	9q2.5	Eggen et al. (1992a)
BL1134	10q3.5-3.6	Smith et al. (1997)
INRA177	11q1.6	Vaiman et al. (1994b)
IDVGA-3	11q2.3	Mezzelani et al. (1995)
LGB	11q2.8	Hayes and Petit (1993)
IDVGA-57	12q1.3	Mezzelani et al. (1995)
IDVGA-41	12q1.5	Mezzelani et al. (1995)
BMC1222	13q1.2-1.3	Hawkins et al. (1995)
ETH7	13q2.1-2.2	Solinas-Tolda et al. (1993)
BL42	13q2.2	Grosz et al. (1997)
TG	14q1.2-1.6	Threadgill and Womack (1990)
BL1036	14q2.3-2.4	Smith et al. (1997)
PTH	15q2.2-2.7	Fries et al. (1988)
HBB	15q2.2-2.7	Fries et al. (1988)
FSHB	15q2.4-qter	Hediger et al. (1991)
IDVGA-10	15q2.5	Mezzelani et al. (1995)
IDVGA-32	15q2.5	Mezzelani et al. (1995)
IDVGA-68	16q1.6	Mezzelani et al. (1995)
IDVGA-49	16q1.7	Mezzelani et al. (1995)
IDVGA-26	16q2.1	Mezzelani et al. (1995)
IDVGA-69	16q2.1	Mezzelani et al. (1995)
ETH11	16q2.1	Solinas-Toldo et al. (1993)
IDVGA-40	17q2.3	Mezzelani et al. (1995)
IDVGA-31	18q1.2-1.3	Mezzelani et al. (1995)
IDVGA-55	18q2.4-dist	Mezzelani et al. (1995)

**Table 1.** (Continued)

Marker	Physical location	Reference
IDVGA-46	19q1.6	Mezzelani et al. (1995)
KRT10	19q1.6	Fries et al. (1991)
ETH12	19q1.7	Solinas-Toldo, et al. (1993)
CIOBT34	19q2.1	Olsaker et al. (1996)
IDVGA-48	19q2.1	Mezzelani et al. (1995)
IDVGA-44	19q2.2	Mezzelani et al. (1995)
ETH3	19q2.3	Solinas-Toldo, et al. (1993)
IDVGA-45	21q1.5	Mezzelani et al. (1995)
UWCA4	21q1.7	Sun et al. (1993)
IDVGA-30	21q2.3	Mezzelani et al. (1995)
IDVGA-39	21q2.3-prox	Mezzelani et al. (1995)
FAS	26q1.3	Yoo et al. (1996)
IDVGA-59	26q2.2	Mezzelani et al. (1995)
BM203	26q2.3	Masabanda et al. (1996)
IDVGA-29	28q1.3	Mezzelani et al. (1995)
BMC1002	28q1.4	Hawkins et al. (1995)
IDVGA-43	28q1.7	Mezzelani et al. (1995)
IDVGA-8	28q1.8-1.9	Mezzelani et al. (1995)
BMC8012	29q1.5 (25q1.5) <sup>b</sup>	Hawkins et al. (1995)
BMC3224	29q1.8-1.9 (25q2.3-2.4) <sup>b</sup>	Hawkins et al. (1995)
BMC1206	29q1.9 (25q2.4) <sup>b</sup>	Hawkins et al. (1995)
IDVGA-7	29q1.9 (25q2.4) <sup>b</sup>	Mezzelani et al. (1995); Eggen et al. (1994)
BMS631	Xp2.4	Sonstegard et al. (1997a)
BL1098	Xp1.4	Smith et al. (1997)
XBM7	Xp1.1	Sonstegard et al. (1997a)
XBM111	Xq1.1	Sonstegard et al. (1997a)
BM4604	Xq2.6-3.1	Yeh et al. (1996)
BMC6021	Xq2.7	Sonstegard et al. (1997a)
INRA030	Xq4.32	Ponce de Leon et al. (1996); Yeh et al. (1996)
UWCA1	23q1.4-1.5	Sun et al. (1993)
HSP70-1	23q2.2	Gallagher et al. 1993
BL6-1	24q1.2	Grosz et al. (1997)
BMC4216	25q1.3 (29q1.3) <sup>b</sup>	Hawkins et al. (1995)

<sup>a</sup>Reported as 6q3.1, but linkage data suggest that it is on chromosome 4.

<sup>b</sup>The nomenclature for chromosome 25 and 29 linkage groups and physical assignments has been interchanged to be consistent with Robertsonian 1:29 translocation data (Eggen et al. 1994; Popescu et al. 1996; Schmutz et al. 1996). The new, physical assignment nomenclature is indicated in parenthesis.

ber of double crossovers detected in the BTA11 linkage group probably reflects genotyping errors. The total number of double crossovers (680) within 20-cM intervals is ~10 times the number (66) reported for swine by Rohrer et al. (1996) but significantly less than a simulated estimate (1033 double crossovers) based on 10,000 replications with no crossover interference and a similar number of genotypes as the current map (1250 linked markers and 185 progeny). The higher number of double crossovers in the bovine map than the porcine map is partially

explained by a threefold larger bovine data set (313,000 vs. ~100,000 genotypes), but the presence of a larger number of genotyping errors in the bovine dataset cannot be discounted.

Five (0.002%; 5/313,000) non-Mendelian inheritance events were detected that could only be explained by a mutation. This mutation rate is less than the dinucleotide repeat mutation rate reported for humans ( $4.5 \times 10^{-4}$ ; Zahn and Kwiatkowski 1995). It is likely that additional dinucleotide repeat mutations were not detected because they appear to be a genotyping error.

**Table 2. Locus Designation of Markers Associated with Coding Sequences**

Marker name	Chr.	Gene name
TF	1	transferrin
ALPI	2	intestinal alkaline phosphatase
EAL	3	erythrocyte antigen L
FCGR2	3	Fc fragment of IgG, low affinity receptor II
G-CSFR	3	colony-stimulating factor receptor
OB	4	leptin
L18952	4	T-cell receptor, V-region
MYF-5	5	myogenic factor 5
BMC1009 <sup>a</sup>	5	KRT, Keratin genes
IGF-1	5	insulin-like growth factor I
CSN3	6	$\kappa$ -casein
CSN1S1	6	$\alpha_{s1}$ -casein
ALB	6	albumin
GC	6	vitamin D-binding protein
IL4	7	interleukin-4
RASA	7	RAS p21 protein activator (GTPase activating protein)
CALPASTAT	7	calpastatin
BRN	10	brain ribonuclease
EAZ	10	erythrocyte antigen Z
IL-R1	11	interleukin receptor, type I
IL-R2	11	interleukin receptor, type II
LGB	11	lactoglobulin, $\beta$
EAB	12	erythrocyte antigen B
TG	14	thyroglobulin
CA2	14	carbonic anhydrase II
ADCY2	15	calmodulin-independent adenylyate cyclase
EAA	15	erythrocyte antigen A
PTH	15	parathyroid hormone
HBB	15	hemoglobin, $\beta$
POTCHA	15	potassium channel protein
FSHB	15	follicle-stimulating hormone, $\beta$ subunit
EAR'	16	erythrocyte antigen R'
EAC	18	erythrocyte antigen C
KRT10	19	cytokeratin class I gene cluster
PTF2	19	post-transferrin factor 2
GFAB	19	glial fibrillary acidic protein
GH	19	growth hormone
MAP2C	19	microtubule-associated protein 2
EAT'	19	erythrocyte antigen T'
ANPRC	20	atrial-natriuretic peptide C receptor
EAS	21	erythrocyte antigen S
HMH1R	22	histamine receptor, H1 subclass major histocompatibility complex, DI $\beta$
BOLA-DIB	23	vascular endothelial growth factor
VEGF	23	erythrocyte antigen M
EAM	23	70-kD heat-shock protein
HSP70-1	23	major histocompatibility complex, class II, DR $\beta$ I
BOLA-DRB1	23	

**Table 2.** (Continued)

Marker name	Chr.	Gene name
BOLA-DRB2	23	major histocompatibility complex, class II DR $\beta$ II
CYP21	23	cytochrome P450, subfamily XXI (steroid 21-hydroxylase)
L29386	23	major histocompatibility complex, class I
PRL	23	prolactin
PAI	25	type-1 plasminogen activator inhibitor
FAS	26	Fas/APO-1
RBP3	28	retinol-binding protein 3, interstitial
OCAM	29	opioid-binding and cell adhesion molecule

<sup>a</sup>Sequence homology to bovine keratin genes as determined by Vaiman et al. (1996).

## DISCUSSION

This second-generation bovine linkage map represents a fourfold increase in map resolution (2.5 cM average interval) over the previous highest resolution bovine map (10.6 cM; Bishop et al. 1994). Six hundred twenty-seven new markers were linked to 623 markers with previous linkage information to provide a basis for integrating the four published bovine maps. In addition to the 313 markers in our previous map (Bishop et al. 1994), the current map contains 70% (119/171), 78% (211/269), and 47% (75/159) of the markers reported by Barendse et al. (1994), Ma et al. (1996b), and Georges et al. (1995), respectively. This map can be utilized easily in many different resource populations at different locations because 98.6% (1233/1250) of the markers are PCR based, with all but two being microsatellites.

Linkage group distances were compared with common markers between the current map and previously published maps to evaluate error detection capabilities with a higher marker density map. The 24% (Barendse et al. 1994; 1677/1348 cM) and 13% (Bishop et al. 1994; 2463/2178 cM) smaller size of the current map compared with the two previous sex-averaged maps was expected, as error detection improves as marker density increases (Lincoln and Lander 1992). The current map is 6% smaller (Ma et al. 1996b; 1730/1625 cM) and 5% larger (Georges et al. 1995; 971/1017 cM) than the two male maps. Male maps are expected to be shorter than a comparable sex-averaged map because of sex-specific differences in recombination rates (Davisson et al. 1989).

Although sex-specific differences in recombination rates have been reported for cattle (Beever et al. 1996), pigs (Archibald et al. 1995), and humans (Dracopoli et al. 1991), the sex-specific difference of the current map (female, 2879 cM; male, 2808 cM) is considerably smaller than the 1.9:1 (female/male) ratio reported for humans by Matisse et al. (1994). Apparent differences in sex-specific map lengths can result from inadequate sex-specific coinformative meioses. Initial analysis of the current data set (185 progeny) indicated a 2907-cM male map and a 2879-cM female map. Closer examination of the data revealed a 100-cM interval between AGLA17 and BM6438 (BTA1) in the male map, whereas only a 1.3-cM interval was observed in the female map. Because the 100-cM interval was supported by only three male informative meioses for AGLA17 and the 1.3-cM female interval was supported by 75 informative meioses, the 100-cM male interval was adjusted to 1.3 cM ( $2907 - 98.7 = 2808$  cM). The small difference (71 cM) in the current sex-specific maps does not preclude sex-specific differences in certain regions of the genome.

As linkage maps continue to develop and additional markers improve the resolving power of the map, genotyping errors also accumulate, introducing spurious recombination events that inflate the linkage group length. As the error rate increases, the statistical support for correct marker order decreases (Ott 1977; Buetow 1991; Morton 1991). The ability to detect genotyping errors improves as marker density increases (Buetow 1991), but the adverse effects of a given error rate also increase with higher marker

**Table 3. Sources of Published Markers**

Markers and marker prefixes	Reference
<i>Random bovine microsatellites</i>	
AGLA, TGLA, MGTG	Georges and Massey (1992)
ILSTS005-ILSTS104, MILSTS076, 080, 083	Guérin et al. (1994); Kemp et al. (1995)
INRA013-INRA200, INRABERN162, 169; INRAMTT183, Hel6	Vaiman et al. (1994a,b, 1995); Velmala et al. (1995)
INRA133, 138, 145, 175, 185, 189, 192, 193, 194, 196, 199; X67827 <sup>b</sup>	D. Vaiman, D. Mercier, K. Moazami-Goudarzi, A. Eggen, and H. Levéziel (pers. comm.)
RM051, 066, 088, 103, 113, 153; RME01, 23, 25	Kossarek et al. (1995a,b); Grosse et al. (1995)
RM065, 090, 094, 099, 127, 137, 150, 151, 156, 169, 186, 194, 214, 215, 216, 222, 232, 301, 309, 310, 320, 321, 323, 326, 327, 338, 350, 356, 363, 372, 379, 388, 404	McGraw et al. (1997)
URB	Ma et al. (1996a)
TEXAN	Holder et al. (1994); Burns et al. (1995)
UWCA	Sun et al. (1994, 1995); Kirkpatrick et al. (1995)
AR026, 028	Avraham et al. (1993a,b)
HAUT1, 14	Thieven et al. (1995)
AFR227, 2215	Jørgensen et al. (1995)
JAB1, 4, 8	Williams et al. (1995)
HUMM2-21, M97201 <sup>a</sup>	M.O. Mosig, A. Shalom, A. Friedmann, and M. Soller (pers. comm.)
BMS4000-BMS4052	Sonstegard et al. (1997b)
BL	Bishop et al. (1994); Grosz et al. (1997); Smith et al. (1997)
XBM, BM7241, 2227, 2592, BMS500	Ponce de León et al. (1996); Sonstegard et al. (1997b)
BMS3004, 3024 (trinucleotides)	Stone et al. (1996a)
BMC1207, 2208, 2228, 3221, 4203, 4214, 4228, 5012, 5227, 6004, 6020	S.M. Kappes, G.A. Hawkins, M.D. Bishop, and C.W. Beattie (in prep.)
BM1815	Morkos et al. (1994)
AF	Konfortov et al. (1996)
X82261 <sup>a</sup> , X82432 <sup>a</sup>	B.A. Konfortov, C.B. Jorgensen, P.D. Thomsen, N.G.A. Miller, J.R. Miller, and W. Barendse (pers. comm.)
<i>Random sheep microsatellites</i>	
MCM	Hulme et al. (1994, 1995); Smith et al. (1995)
OarCP39	A.M. Crawford (pers. comm.)
OarHH, OarAE, OarFCB, OarEL, OarJMP, OarCP, MAF <sup>b</sup>	Buchanan et al. (1994); Ede et al. (1994); Pierson et al. (1994); Crawford et al. (1995); Lord et al. (1996)
<i>Microsatellites associated with genes</i>	
L18952 <sup>a</sup> (T-cell receptor, V-region)	J. Buitkamp, F.-W. Schwaiger, and J.-T. Eppler (pers. comm.)
ALPI (L07733 <sup>a</sup> , intestinal alkaline phosphatase)	Weissig et al. (1993); T.S. Sonstegard, N.L. Lopez-Corrales, S.M. Kappes, C.W. Beattie, and T.P.L. Smith (in prep.)
POTCHA (X57033 <sup>a</sup> , potassium channel protein)	Garcia-Guzman et al. (1992)
M85278 <sup>a</sup> (bovine dinucleotide repeat polymorphism)	A. Avraham, O. Yoffe, M. Bard, M. Shani, and M.M. Ron (pers. comm.)
IL4 (interleukin-4)	Buitkamp et al. (1995)
L29386 <sup>a</sup> (class I, BoLA)	Skow et al. (1994)
BM1500, BM1501 (leptin)	R.T. Stone, S.M. Kappes, and C.W. Beattie (unpubl.)
FSHB (follicle-stimulating hormone, $\beta$ -subunit)	Kemp and Teale (1991)
FAS (Fas/APO-1)	Yoo et al. (1996)



**Table 3.** (Continued)

Markers and marker prefixes	Reference
<i>Restriction fragment length polymorphisms</i>	
IL1-R1, IL1-R2 (interleukin receptor, type I, II)	Yoo et al.(1994)
G-CSFR (colony-stimulating factor receptor)	Yoo et al. (1995)
DIB (BoLA, DIB)	Morkos et al. (1994)
OBS (leptin)	Stone et al. (1996b)
TG (thyroglobulin)	Daskalchuk and Schmutz (1997)
CSN1S1 ( $\alpha_{s1}$ -casein)	David and Deutch (1992)
Markers not listed in Tables 1 and 3 have been referenced in one of the following: Barendse et al. (1994); Bishop et al. (1994); Moore et al. (1994); Stone et al. (1995, 1997).	
<sup>a</sup> GenBank accession number.	
<sup>b</sup> In original publications, some of the sheep markers were lacking the Oar prefix.	

density (Lincoln and Lander 1992). Consequently, intensive correction of genotyping errors in dense maps results in large reductions of map length and improved marker order. We considered genotypes causing two or more recombination events in a small chromosomal region (<20 cM) as potential genotyping errors. A second PCR reaction was genotyped for the potential errors, correcting 0.33% of the total genotypes (1026/313,000) and reducing total map length by 23% (3680/2990 cM). Genotypes validated by a second PCR reaction and still causing unlikely recombination events were maintained in the data set because it may be indicative of other genotyping errors or an incorrect marker order.

Estimates of bovine genome size range from 3000 (Fries and Ruddle 1986) to 2820 cM (Barendse et al. 1993). The ratio of chiasmata to genome length (2 chiasmata/cell = 1 Morgan; 2:1) used to estimate genome length for bulls presents an unlikely cow genome size (1.8 M); therefore, the 1.135:1 ratio observed in women was used for cows (Barendse et al. 1994). Although the current map (2990 cM) is similar to the Fries and Ruddle (1986) estimate and slightly larger than the Barendse et al. (1993) estimate, it is likely that our data set still contains undetected genotyping errors and the map does not represent complete coverage of all 30 chromosomes. A more robust estimate of genome size and coverage can be made when polymorphic markers from the ends of linkage groups are physically assigned to chromosomes.

The fourfold increase in marker density of the current map allows for an efficient genome-wide QTL search, but additional markers will be needed in regions flanking QTL for efficient MAS. Marker density in regions containing QTL is likely to be one of the limiting factors in resolving QTL location and

efficiency of MAS because < 60% of the markers on the current map are informative within a  $F_1$  *B. taurus* animal and 14% (177/1220) of the intervals are greater than the 10-cM maximum suggested by Ott and Donis-Keller (1994).

Unfortunately, livestock mapping resources are currently targeted toward QTL detection, and additional large-scale development of random markers appears to be unlikely in the near future. Several strategies exist for generating additional markers for specific regions of the genome containing QTL. These include microdissected, microcloned libraries (Ponce de León et al. 1996; Sonstegard et al. 1997a,b) and identification of YAC clones (Smith et al. 1997) containing the closest flanking markers to the QTL. Additional microsatellites can be identified within a YAC clone (Lench et al. 1996) for haplotyping to increase the polymorphic content of a marker locus to the extent that it is informative in almost every animal. Comparative mapping information from human and mouse genome mapping efforts can also improve QTL mapping efficiency by providing candidate genes based on location and function. Comparative mapping within Bovidae families can improve the respective linkage maps and QTL detection because cattle and sheep microsatellites have been used reciprocally in cattle, sheep, and goat maps (Barendse et al. 1994; Bishop et al. 1994; Crawford et al. 1995; Vaiman et al. 1996; M.G. de Gortari, B.A. Freking, A.M. Crawford, S.M. Kappes, R.T. Stone, and C.W. Beattie, in prep.). Marker order appears virtually identical between sheep and cattle and very similar between goat and the other two species (Vaiman et al. 1996; S.M. Kappes, M.G. de Gortari, B.A. Freking, A.M. Crawford, R.T. Stone, J.W. Keele, K. Dodds, and C.W.

**Table 4. Parameters of the Bovine Linkage Map**

Chromosome	No. of loci <sup>a</sup>	Length <sup>b</sup> (cm)	Avg. interval (cm)	No. of double crossovers <sup>c</sup>	Percent of genome <sup>d</sup>	Expected length (cm) <sup>e</sup>
1	102/58	153	1.5/2.6	43	5.87	176 (-13)
2	62	120	1.9	8	5.12	154 (-22)
3	64	127	2.0	34	4.71	141 (-10)
4	46	108	2.3	32	4.67	140 (-23)
5	45	133	3.0	58	4.48	134 (-1)
6	50/49	126	2.5/2.6	29	4.33	130 (-3)
7	41	137	3.4	31	4.18	125 (+9)
8	38	124	3.2	32	4.13	124 (0)
9	52	108	2.1	22	3.86	116 (-6)
10	47	105	2.2	23	3.67	110 (-5)
11	68	129	1.9	60	3.94	118 (+9)
12	35	105	3.0	24	3.29	99 (+6)
13	34	87	2.6	7	3.09	93 (-6)
14	35	89	2.5	28	3.15	95 (-6)
15	39	109	2.8	49	3.11	93 (+17)
16	38	94	2.5	22	3.07	92 (+2)
17	31	99	3.2	6	2.83	85 (+17)
18	39	81	2.1	10	2.60	78 (+4)
19	37	100	2.7	9	2.54	76 (+31)
20	28	75	2.7	5	2.75	83 (-9)
21	35	94	2.7	26	2.72	82 (+16)
22	28	79	2.8	14	2.51	75 (+5)
23	30/29	68	2.3/2.3	23	2.09	63 (+8)
24	29	61	2.1	7	2.37	71 (-14)
25 <sup>f</sup>	23/22	71	3.1/3.2	9	1.99	69 (+18)
26	25	72	2.9	20	1.96	59 (+22)
27	25	64	2.6	20	1.83	55 (+17)
28	27	52	1.9	8	1.73	52 (+1)
29 <sup>f</sup>	32	69	2.2	8	1.97	59 (+17)
X	65/48	151	2.3/3.1	16	5.45	163 (-8)
Total	1250/1186	2990	2.4	680		

<sup>a</sup>The second number does not include 64 markers generated from chromosome 1, Xp, and Xq microdissected libraries (Ponce de León et al. 1996; Sonstegard et al. 1997a,b).

<sup>b</sup>All values are for a sex-averaged map except the X chromosome value, which is a female map length.

<sup>c</sup>Number of double recombination events detected within 20-cM intervals, including double recombination events supported by more than one genotype.

<sup>d</sup>Estimate of chromosome size relative to total genome was reported by Popescu et al. (1996).

<sup>e</sup>Expected length was calculated by multiplying the percent of genome by 3000 cM. Numbers in parentheses represent the percent difference between actual and expected (actual/expected).

<sup>f</sup>The nomenclature for the chromosome 25 and 29 linkage groups has been interchanged to be consistent with Robertsonian 1:29 translocation data (Eggen et al. 1994; Popescu et al. 1996; Schmutz et al. 1996).

Beattie, unpubl.). QTL detected in one species may be useful for understanding the biology of a trait with a similar phenotype in the other two species.

In summary, the current map represents a considerable improvement in bovine map resolution that will enhance QTL detection and subsequent MAS or positional cloning. Additional markers will

likely be needed in specific regions of the genome that contain QTL, but strategies are available to increase marker density in those regions. The usefulness of this linkage map extends beyond cattle, to sheep and goats, where it is unlikely that a large number of additional markers will be generated in the near future.

## METHODS

### Data Collection

Markers were genotyped across the MARC reference population (Bishop et al. 1994). Genomic DNA was obtained from whole blood by the salt extraction method described previously by Miller et al. (1988). Conditions used to amplify specific segments of genomic DNA were consistent with Bishop et al. (1994) while reducing the quantity of DNA per reaction to 50 ng. Amplified products were [ $\alpha$ - $^{32}$ P]dATP labeled by random incorporation, or one of the primers was end labeled to reduce sub-banding. Primer pairs were occasionally multiplexed when sizes and PCR conditions allowed. Gel electrophoresis and scoring of grandparental, parental, and progeny genotypes were performed essentially according to Bishop et al. (1994). Genotypes were independently scored twice and discrepancies resolved. All primer sequences were reported previously (Table 2).

### Data Analyses

Markers were placed into linkage groups based on two-point lod (>3.0) scores and ordered within the group using multipoint linkage analysis (CRI-MAP v. 2.4; Green et al. 1990). New markers were added to linkage groups with the ALL option by inserting the markers with the largest number of informative meioses first. The FLIPS option was used after inserting three to four markers per linkage group to evaluate local marker order. Two-point linkage information and sheep linkage mapping information (M.G. de Gortari, B.A. Freking, A.M. Crawford, S.M. Kappes, R.T. Stone, and C.W. Beattie, in prep.) were used to determine marker order for markers that inflated the linkage group >20 cM. Linkage groups were periodically rebuilt with the BUILD option by inserting markers in decreasing informative meioses order. After preliminary alignment, the CHROMPIC option was used to identify unlikely double crossovers.

The CHROMPIC option worked well for identifying genotypic errors in progeny but was less effective in identifying parental and grandparental genotypic errors. Family recombination rates were compared to identify potential parental and grandparental genotyping errors. Genotypes causing double crossovers were rescored from a second PCR reaction as advised by Buetow (1991) and entered into an interactive relational database (Keele et al. 1994). The FLIPS option was used subsequent to error corrections to determine marker order with the highest log likelihood.

Linkage groups containing a number of markers with like-heterozygote genotypes for the sire, dam, and progeny (identified as switches in CRI-MAP 2.4) could not be analyzed because of computational requirements. Markers containing a large number (>20) of like-heterozygote genotypes were removed from the initial multipoint analysis to determine marker order of the remaining markers. Markers containing like-heterozygote genotypes were included in the final analysis, but like-heterozygote genotypes of the progeny were removed from families contributing the largest number of computationally demanding genotypes.

Common linkage group distances were calculated from the current map and different published maps (Barendse et al. 1994; Bishop et al. 1994; Georges et al. 1995; Ma et al. 1996b) using the two most external common markers for each linkage group. Linkage groups that did not contain two or more

common markers between the current map and a published map were not included in the comparison.

Marker heterozygosity was determined only for parents of the reference mapping population by dividing the number of heterozygous genotypes by the total number of markers genotyped per animal. Heterozygosity values were averaged across animals of similar breed type with each animal weighted equally. The heterozygosity formula of  $1 - \sum(P_i)^2$  was not used as 1–13 animals per breed type was not considered sufficient to give a reliable estimate of allele frequency.

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