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An integrated genetic and physical map of the bovine X Chromosome

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Abstract. Genotypic data for 56 microsatellites (ms) generated from maternal full sib families nested within paternal half sib pedigrees were used to construct a linkage map of the bovine X Chromosome (Chr) (BTX) that spans 150 cM (ave. interval 2.7 cM). The linkage map contains 36 previously unlinked ms; seven generated from a BTXp library. Genotypic data from these 36 ms was merged into an existing linkage map to more than double the number of informative BTX markers. A male specific linkage map of the pseudoautosomal region was also constructed from five ms at the distal end of BTXq. Four informative probes physically assigned by fluorescence in situ hybridization defined the extent of coverage, confirmed the position of the pseudoautosomal region on the q-arm, and identified a 4.1-cM marker interval containing the centromere of BTX.

Introduction

One prerequisite to identifying quantitative trait loci (QTLs) is a genetic map with sufficient informative markers to maximize genome coverage. Since meioses and marker heterozygosity may limit map development and resolution of a QTL within a resource population, a high density of informative markers ensures flexibility in selection of markers for genomic scans of exogenous germplasm. The majority of genetic markers on current livestock maps are microsatellites (Weber and May 1989) generated from randomly cloned DNA. Several hundred of an estimated 44,000 ms in the bovine genome (Stone et al. 1995) have been linked in low-resolution linkage maps (Barendse et al. 1994; Bishop et al. 1994). These maps are sufficient to identify large chromosomal regions containing QTLs, but are not sufficient for either fine mapping of a QTL or marker-assisted selection (MAS) within and between bovine breeds. Continued development of markers from random genomic libraries is inefficient for increasing marker density in specific regions of the genome. A more efficient strategy of obtaining chromosome/region-specific markers is to screen libraries containing small DNA inserts microdissected and microcloned from metaphase chromosomal spreads (Ludecke et al. 1989). Microdissected libraries have increased marker density in specific genomic regions for a number of species (Greenfield and Brown 1987; Weber et al. 1990; Fiedler et al. 1991; Bahary et al. 1993; La Pillo et al. 1993; Seki et al. 1993; Kobayashi et al. 1995; Ponce de León et al. 1996).

The bovine X Chr has proven to be the most difficult chromosome to assemble a linkage map adequate for QTL analysis. A very large population is required to develop a BTX linkage group, because only female meioses are informative at a level of 60% (marker heterozygosity) for *F₁ Bos taurus × Bos taurus* (Bishop et

al. 1994). Barendse and associates (1994) reported a BTX linkage map that contained three linked loci anchored by physical assignment of the heterozygous loci, *TGLA325* and *MAF45*, to Xp14-ter, which suggested the pseudoautosomal region (PAR) was located at the distal end of Xp. In contrast, fluorescent in situ hybridization (FISH) with a bovine Y Chr specific paint suggested the bovine PAR was located at Xq4 (Ponce de León and Carpio 1995). This reorientation of the PAR was subsequently supported by assignment of *INRA030* to Xq42-ter, a heterozygous locus closely linked to *TGLA325* on the two most recent linkage maps of BTX (Ponce de León et al. 1996; Yeh et al. 1996). The human and bovine X Chr are estimated at approximately 150 cM (Harnden and Klinger 1985). Ponce de León and colleagues (1996) reported spanning 89.4 cM (ave. interval 6.0 cM) of BTX with the majority of markers developed from a microcloned library of Xq. The BTX map of Yeh and coworkers (1996) covers 118.7 cM (ave. interval 7.9 cM), with sufficient genotypic data to construct a male-specific linkage map of the PAR (13.0 cM; ave interval 3.3 cM). Unfortunately, none of the loci on either linkage map was physically anchored to Xp, which would have supported extensive coverage of BTX.

We increased assigned marker density of the X Chr in two steps to provide a high-resolution genetic map and verify extent of coverage. First, a BTXp-specific lambda library was screened for ms from the marker-deficient region of BTX. Loci which appeared to be linked near the telomeres and centromere of BTX were selected for physical assignment. We report an increase in marker density for BTX almost fourfold higher than previously reported (Ponce de León et al. 1996; Yeh et al. 1996), construction of a male-specific linkage map, and four physical assignments of BTX-linked loci that confirmed coverage. These results offer a comprehensive map of BTX that will ultimately enhance QTL analysis of this chromosome.

Materials and methods

Acquisition of microsatellites. Methods used to obtain ms markers from M13 bacteriophage libraries (BM and BMS series) and genomic lambda clones (BL series), have been described previously (Bishop et al. 1994; Stone et al. 1995; Smith et al. 1996b). Preparation of the BTXp microdissected library and ms identification from the BTXp library were as described (Ponce de León et al. 1996), with some modification. BTXp lambda clones were screened with a (GT)₁₁ radiolabeled probe at high stringency conditions (65°C) as described (Stone et al. 1995), and sequenced according to the manufacturer's protocol (Sequenase, U.S. Biochemicals, Cleveland, Ohio). All sequenced clones were searched for similarity against: 1) repetitive sequences (Alexander et al. 1995; Stone et al. 1995); 2) ms identified in our laboratory (Bishop et al. 1994; Stone et al. 1995; Ponce de León et al. 1996; Smith et al. 1996b); and 3) ms recorded in GenBank (Benson et al. 1993) with software from the Genetics Computer Group, Madison, Wisconsin (GCG, 1994). Primer pairs were designed only from unique clones containing (GT) > 11. PCR conditions, allele sizes, and heterozygosity were determined for each ms primer pair as described (Bishop et al. 1994; Stone et al. 1995).

Linkage analysis. Genotypic data for each ms marker obtained from the U.S. Meat Animal Research Center (MARC) reference population (Bishop et al. 1994) was independently scored, verified, and entered into an interactive database (Keele et al. 1994). The linkage map was constructed in two phases. First, verified genotypes were placed into a BTX linkage group on the basis of two-point LOD (>3.0) with the ALL option of CRI-MAP 2.4 (Green et al. 1990). Markers were added to this linkage group as the genotypes were verified and were continually ordered within the group with the FLIPS option. After the linkage group was constructed, markers with the most meioses were ordered onto a framework linkage map with the BUILD option (LOD > 5.0). Then, the markers (LOD > 3.0) were added to complete a framework linkage map. Any remaining markers were entered individually according to number of informative female meioses with ALL (LOD > 3.0) and FLIPS5 options after every three markers, respectively. Unlikely double recombinants were evaluated, and genotypes reassessed when necessary.

Fluorescence in situ hybridization (FISH). Metaphase chromosomes were prepared as reported (DiBerardino and Iannuzzi 1982). FISH analyses of bovine lambda DNA were performed essentially as described (Lichter et al. 1990; Ponce de León et al. 1996). Briefly, probes were biotinylated with Bionick (Boehringer-Mannheim, Indianapolis, Ind.) and purified through a G-50 fine sephadex column (Pharmacia, Piscataway, N.J.). Approximately 150 ng of labeled probe was co-precipitated in ethanol with 5 µg sonicated salmon sperm DNA and either 5 µg sheared bovine genomic or Cot 1 DNA. For FISH analysis of the bovine YAC probe BY289/F3, 1–1.5 µg of labeled total yeast DNA and 10 µg of Cot1 DNA were used in the hybridization mix for each slide. Metaphase spreads from four animals were used to analyze each probe.

Isolation of probes for FISH. Genomic lambda clones were isolated from a bovine lambda Dash library (Stratagene, La Jolla, Calif.) by an iterative screen/PCR-based method (Israel 1993; Heaton and Smith unpublished). Lambda PCR reactions (11 µl) were performed on microtiter plates as previously described (Bishop et al. 1994). A typical reaction mix was composed of 1 µl lambda/NZY supernatant, 1 µM of each primer, 10 mM Tris-HCl (pH 9.0), 50 mM KCl, 0.1% Triton X-100, 91 µM dNTPs, 1.5 mM MgCl₂, 625 ng RNase A (Sigma, St. Louis, Mo.), and 1 U *Taq* DNA polymerase (Promega, Madison, Wis.). Bovine YACs were screened by PCR and isolated from total yeast DNA as described (Bentley et al. 1992; Smith et al. 1996a). Lambda DNAs were isolated from lid lysates according to the manufacturer's protocol (Quiagen, Chatsworth, Calif.).

Results

Seven unique ms markers were generated from the BTXp microdissected library (Table 1) containing 3.22 Xp chromosome equivalents (Ponce de León et al. 1996). Approximately 1×10^5 plaques (one p-arm equivalent of DNA) screened at high density with (GT > 11) yielded 125 plaques (0.13%). When replated at low density and screened under the same conditions, 73 plaque isolates (0.07%) remained positive and contained ms. Forty-one clones were excluded from sequencing after restriction enzyme analysis revealed a redundancy for clones containing sequences homologous too HUMm2-21, XBM451, and XBM171 (data not shown). The remaining 32 clones were sequenced, and 13 of these (0.013% of clones screened) yielded unique ms sequences (data not shown). Sequence searches showed one of these 13 clones to be to HUMm2-21, a previously unlinked ms (Mosig et al. 1992). Primer pairs (XBM series) designed from the flanking sequence of the 12 remaining ms were tested on the MARC reference map parents. Eight of the primer pairs amplified an allele size predicted from sequence analysis, and seven were polymorphic (Table 1). These XBM markers were scorable, and displayed obvious sex-linked inheritance with the exception of *XBM451*, which was found to lie within the PAR region of BTX.

The BTX linkage map was generated from the MARC map reference population (415 potential meioses; 203 potential female meioses; Bishop et al. 1994). BTX-linked loci were identified with female-specific, two-point LOD scores (LOD > 3.0) to an existing BTX linkage group (Kappes unpublished). This linkage group was initially composed of 15 ms from the linkage map of Ponce de León et al. (1996) and five ms previously linked to BTX (Bishop et al. 1994). The 36 previously unlinked ms added to this linkage group included seven XBM ms from the BTXp library, and 29 ms markers developed from various genomic libraries (see Fig. 1). Four of the ms (*BM7241*, *BMS2227*, *BMS2592*, and *BMS500*) isolated from genomic M13 libraries (Stone et al. 1995) were previously unpublished (Table 1).

The linkage map was reconstructed to place markers within the map according to number of informative meioses, with the final map consisting of 56 ms loci which spanned 150.5 cM (ave. in-

Table 1. Type II loci (ms) generated from clones obtained from random, genomic M13 libraries and the Xp chromosome specific library.

Locus ^a	Forward (top) and reverse (bottom) primer sequences (5' → 3')	Annealing Temp. (°C)	Allele (bp) Max.-Min.	No. alleles
<i>XBM111</i> ^b	TGAAAGGGGATGACTTACAAC AATCGCAAGAGTGGGACAC	58	133–131	2
<i>XBM142</i> ^b	AATACCATGGACAGAGAGCC CTCTGCTGAGTGGGGTG	58	195–185	4
<i>XBM361</i>	ACACACTGAGAATTAACTACAAAAACC ACACAACCTGAAGCCACTTTAAGC	58	157–147	5
<i>XBM411</i>	AGTCACGAAATGCCACATG GTTCAAGATTACCACCATAGCC	58	197–178	8
<i>XBM451</i>	GTATCCATCCACAGGGTTGC TATGTAGGGACAGCCCCATCC	58	122–106	7
<i>XBM491</i> ^c	CTGGGTGACAGGAGTGAGAC ATCACAAATTTAAGCAGAAGATAGG	50	190	1
<i>XBM521</i>	CCTTCAGGTCTCAGCTCACC AGTGCTATGAAGAAGACAGGG	58	127–123	3
<i>XBM701</i>	TTCCCTTGAAATCATCTGG TCCAAGTTACCAAAATTGACCC	58	161–151	4
<i>BM7241</i>	ATCAGAGACCTGAAAGCACTCA GCAGAGGATTTAGCTCCAGC	58	150–120	12
<i>BMS2227</i>	AAATTTGCTATTTCTCTAGACATGATT ATGGTTATTTTCATAATCAGAGGTATG	58	176–158	8
<i>BMS2592</i>	GAGCTGTTCCACATGCAGAT GATGGAGGAGGAATAAGACAGG	58	130–100	6
<i>BMS500</i>	GGGGAGCCAAGATATGGAAG CCATGTTGTCGAGCAATGAC	58	171–163	5

^aPrimers designated XBM are from the BTXp microdissected library, BMS are from M13 enriched libraries, and BM are from M13 bacteriophage libraries.

^bOne primer sequence is similar to A or C SINES.

^cMarker is monomorphic, and linkage is undetermined.

interval of 2.7 cM; Fig. 1). Marker order was identical to that reported by Yeh et al. (1996) for markers common to both maps (*BM6017*, *BM2713*, *BM4604*, *TGLA325*, *MAF45*, *INRA030*). However, the average marker interval between these loci was reduced threefold, and overall coverage of the linkage map was extended 6.7 cM (see *XBM451*, *BMS631*, *ETH123*, and *XBM411* in Fig. 1). Comparison of the interval distance between *BM6017* to *INRA030* revealed a 25.1 cM size difference between the map of Yeh and associates (1996) and the current map (118.7 cM to 143.8 cM, respectively).

The male-specific linkage map contains four male heterozygous loci (*XBM451*, *INRA030*, *MAF45*, and *TGLA325*) linked to the hemizygous markers *XBM31* and *BL22* (Fig. 1). Marker order agrees with that presented by Yeh and colleagues (1996), but the coverage of the current map was extended 8.2 cM by the addition of *XBM451*. The male-specific recombination rate between these four loci was fivefold higher than in females (33.0 to 6.6 cM, respectively) similar to the increased rate of male recombination observed in the pseudoautosomal regions of the human sex chromosomes (Rouyer et al. 1986; Schmitt et al. 1994).

Four loci were selected for physical assignment owing to their

respective location on the BTX linkage map. Two markers, *INRA030* and *BMS631*, which lie near the ends of the linkage map, were chosen to determine the extent of physical coverage by our linkage map (Fig. 1). *XBM7* and *XBM111* were chosen as markers to localize the centromere of X owing to their proximity to *BL1098* (Fig. 1; 3.5 cM and 7.6 cM, respectively) previously assigned to Xp14 (Smith et al. 1996b). Primer pairs for these four loci were screened across a genomic lambda library (*XBM7*, *INRA030*, and *BMS631*) and the USDA/MARC bovine YAC library (*XBM111*) to isolate large insert probes. FISH analyses of these probes are shown in Fig. 2. The assignments of *XBM111* to Xq11 and *XBM7* to Xp11 defined a 4.1-cM interval of the BTX map that spans the centromere. The localization of *INRA030* to Xq42-3 and *BMS631* to Xp24 confirmed extensive coverage of the entire X Chr by the linkage map. Seven loci now integrate the physical and genetic maps of BTX (Fig. 1).

Discussion

Results from our directed strategy increased marker density fourfold over those previously reported (Ponce de León et al. 1996;

Fig. 1. Comparison of physical and genetic maps of bovine X Chromosome. An R-banded ideogram of BTX (left) is next to a linkage map of BTX (150.5 cM). Loci assigned by FISH are indicated by vertical bars next to the ideogram. Genetic distances between loci (>2 cM only) are to the left of the linkage map (cM), and locus names are to the right. Boxed loci indicate markers linked with no detectable recombination. The pseudoautosomal region (PAR) is indicated by the dashed box at the bottom of the linkage map. A 33.1-cM linkage map of the PAR region (Male Specific) is shown to the right of this box. The number of male and female (Fem.) meioses generated for each marker is listed to the far right. Superscripts denote references for ms previously described: (Stone et al. 1995)ᵃ, (Smith et al. 1996)ᵇ, (Ponce de Leon et al. 1996)ᶜ, (Bishop et al. 1994)ᵈ, (Steffan et al. 1993)ᶜ, (Ma et al. 1996)ᶠ, (Georges and Massey 1992)ᵍ, (Mosig et al. 1992)ᵇ, (Sun et al. 1994)ᵃ, (Guerin et al. 1994)ᵃ, (Dietz et al. 1993)ᵃ, and (Ciampolini et al. 1993)ᵃ.

Fig. 2. FISH analysis of four X-linked microsatellite markers. A panel of four bovine metaphase preparations showing FITC hybridization signals of selected loci to the bovine X Chr. Black arrowheads point to the location of the detected fluorescence signal of each probe. The panel displays the following: (a) *INRA030* (lambda clone) to Xq42-43; (b) *BMS631* (lambda clone) probe to Xp24; (c) *XBM111* (YAC clone BY289/F3) to Xq11; and (d) *XBM7* (lambda clone) to Xp11.

Yeh et al. 1996) and defined the boundaries of Xp and Xq. As a result, the BTX map (Fig. 1) differs from previous maps in three respects. First, map resolution was improved threefold with no marker interval larger than 20 cM. Marker intervals of 21.1 cM and 35.8 cM between *BM6017* and *BM4604* reported on the map of Yeh and coworkers (1996) were reduced and refined. Isolation of ms from the BTX-specific libraries reduced larger marker intervals and increased overall marker density within BTX. A total of 17 ms or approximately a third of the markers on the BTX map have been developed from BTX-specific microdissected libraries (10 ms markers from Ponce de León and associates 1996; see XBM markers in bold in Fig. 1). Since the BTX-specific libraries were not exhaustively screened, they continue to serve as a resource for additional ms.

The map of BTX (Fig. 1) is an estimated 25 cM larger than the BTX linkage map of Yeh and coworkers (1996) for two reasons. The slight inflation in genetic intervals between markers common to this map and that of Yeh and associates (1996) can be best explained by the increase in marker density, and the special challenge the sex chromosomes present in detecting errors with only a limited number of coinformative meioses (Murray et al. 1994). The present linkage map (Fig. 1) extends overall coverage of BTX by 6.7 cM.

Extended coverage of the X Chr was confirmed with the assignments of *XBM111*, *XBM7*, and *BMS631*, which integrated the linkage map across most of the physical map of BTX and established genetic boundaries for the q and p arms. Some important observations can be made from these assignments. First, comparison of the linkage and physical maps suggests the recombination rate throughout the X Chr is not homogeneous (Fig. 1). Recombination rates between markers bordering the centromere appear reduced in comparison to the more distal regions of BTX. This observation is supported by the assignment of *BL1098* to Xp14 (Smith et al. 1996b). The linkage distance between *BL1098* and *XBM7* is 3.5 cM, yet physical distance between these markers is approximately equivalent to a fourth of the p-arm (Figs. 1 and 2). Furthermore, these results support the BTX linkage results of Yeh and coworkers (1996) that suggest heterogeneity of recombination for BTX. The observed reduction in recombination near the centromere correlates with that observed for the pericentromeric region of X in humans (Weeks et al. 1995). Linkage distances between markers more distally located on BTXp suggest a region of

elevated recombination exists between *BMS631* and *BL1098*. Interestingly, a recombination hot spot has been mapped on the human X Chr (Xp21) at the Duchenne muscular dystrophy gene (Grimm et al. 1989). Further integration of the bovine linkage and physical maps is needed to substantiate existence of a recombination hotspot(s) within BTX.

This overall increase in BTX-linked markers is a significant improvement of the linkage map, and an essential ingredient of a genome-wide analysis for QTLs (Lander and Kruglyak 1995). The present linkage map (Fig. 1) contains enough highly polymorphic markers to perform higher resolution QTL searches, enhances the efficiency of mapping genes to BTX by RFLP analysis, and ensures the availability of widely distributed and informative loci for interval mapping of BTX within and between breeds.

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