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Development of a linkage map and QTL scan for growth traits in North American bison

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Abstract. PCR protocols incorporating fluorescently labeled multiplexed primer combinations were developed to produce a linkage map for bison. Three hundred fifty eight microsatellite loci spanning all 29 autosomes were genotyped via 83 PCR multiplexes and nine individual amplifications. A total of 292 markers were integrated into an autosomal linkage map for bison. The sex averaged bison map (2,647 cM) was approximately 9% longer than the corresponding USDA MARC map, which covered 2,415 cM. Utilizing weaning, yearling and 17-month weights from two private bison herds, a QTL scan was conducted using the developed linkage map. LOD peaks suggestive of QTL were identified on chromosomes 2, 7, 15, and 24 for weaning weight, chromosomes 4, 14, and 15 for yearling weight and chromosomes 8, 14, and 25 for 17-month weight. Four of the identified chromosomes have conserved synteny with regions harboring growth QTL in cattle.

Bison once numbered in the tens of millions in North America. However, due to the population bottleneck experienced in the late 1800s, their numbers were reduced to not more than 541 individuals by 1888 (Coder, 1975; Dary, 1989). Almost all of the bison alive today can be traced back to five populations that were used to repopulate most of the extant public and private herds (Coder, 1975). Current semi-wild bison populations are fragmented among public parks and sanctuaries throughout the United States and Canada. However, more than 90% of the bison today reside on private ranches where they are raised for meat production. Reduced reproduction and other deleterious manifestations associated with a bottlenecked population are rare in current bison herds (Berger and Cunningham, 1994). The fact that bison went through a severe population bottleneck without suffering catastrophic consequences and are increasingly becoming a viable participant in the livestock industry makes them a unique species for genetic study and comparison to domestic cattle.

The second-generation bovine linkage map of Kappes et al. (1997) contained 1,250 markers with an average marker interval of 2.5 cM. Additional markers have subsequently been added to this map, further increasing marker density and providing a rich resource for genetic studies of bison. However, to date, only three studies report microsatellite variation in North American bison, two of them on a very limited scale (Mommens et al., 1998; Wilson and Strobeck, 1999; Ward, 2000). Genetic evaluations, whether for the purposes of genome scans for economically important genes or conservation biology, require genotyping large numbers of markers across a large number of individuals. Genotyping microsatellites by radioactive methods can be both time-consuming and costly. While microsatellite markers offer the advantage of rapid throughput via co-amplification and simultaneous genotyping of multiple loci, this feature has rarely been utilized because the optimization of multiplex reactions is often more time consuming and difficult than the optimization of PCR for individual loci. However, using the information amassed during construction of the bovine genetic map and fluorescence-based detection, it

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is possible to greatly reduce the time and cost involved in genotyping. Unfortunately, multiplexing on a sufficient scale has not previously been done in cattle or bison for linkage mapping or quantitative trait loci (QTL) scans. The availability of a panel of multiplexed microsatellite markers for rapid genotyping of North American bison and domestic cattle would greatly enhance the feasibility and efficiency of initial QTL scans and of genetic diversity assessments in these species.

Numerous QTL regions have been identified in cattle for traits such as weight and carcass characteristics (Elo et al., 1999; Stone et al., 1999; Grosz and MacNeil, 2001; Kim et al., 2003). Most of these reports utilized experimental crosses to produce a mapping population by crossing lines with large differences in mean phenotype. Forming experimental crosses between divergent lines offers advantages of an increased likelihood of segregating QTL, increased power to detect QTL and ease of analysis, but it also has a very important limitation. These crosses are designed to detect QTL which are fixed, or nearly fixed for alternate alleles between the parental breeds. Thus, the identified QTL are likely to not be segregating in the founder populations that were crossed (Haley 1999). Conversely, mapping within commercial populations offers the advantage that specific crosses need not be made and thus pedigrees and phenotypes can quickly be collected. Additionally, any QTL identified within a commercial population may immediately be incorporated in the breeding program for that population. However, these advantages come at the cost of decreased power of QTL detection and an increase in the computational complexity required to appropriately analyze the phenotypes.

Materials and methods

DNA source

Two private bison herds were used as the source of animals for the mapping and QTL analysis. The Arrowhead Buffalo Ranch herd (ABR) located in Canton, Ohio contained 173 total individuals, 49 parents (43 females, 6 bulls) and 124 offspring (57 females, 67 males). The Hidden Hollow Preserve herd (HHP) located in Bradfordsville, Kentucky contained 40 total individuals, 12 parents (11 females, 1 bull) and 28 offspring (15 females, 13 males). The herds were not known to be related. Genomic DNA was isolated from tail hair follicles or white blood cells by proteinase K treatment followed by phenol:chloroform extraction (Sambrook et al., 1989) or by using the SUPER QUICK-GENE DNA Isolation kit (Analytical Genetic Testing Center, Denver, Colorado).

Microsatellite loci

A total of 358 microsatellite primers were synthesized with a fluorescent label added to each forward primer (Supplementary Appendix A; www.karger.com/doi/10.1159/000075726). Loci were chosen primarily from the USDA MARC cattle mapping database (http://www.marc.usda.gov), but also included other published marker reports. Attempts were made to evenly space the markers on each chromosome and to choose loci with high heterozygosity and a large number of alleles based on cattle data. Additionally, markers were chosen at higher density for chromosomal regions previously reported to harbor growth QTL in cattle. Multiplexes were developed by combining loci with different fluorescent labels and different allele size distributions in domestic cattle. PCR conditions were optimized in an attempt to maximize the number of loci included within a single reaction. Multiplex PCR conditions and thermal profiles can be found in Supplementary Appendices B and C (www.karger.com/doi/10.1159/000075726). All PCR was carried out using a GeneAmp PCR 9700 thermocycler (PE Biosystems). PCR products were separated on an ABI Prism 377 DNA Sequencer or an ABI Prism 310 Genetic Analyzer (PE Biosystems) and were sized relative to an internal size standard (MAPMARKER LOW, Bioventures).

Mapping

A linkage map for each bison autosome was constructed using CRI-MAP v. 2.4 (Green et al. 1990) and the BUILD option by incorporating loci into the map whose order was supported by a LOD score >3. Any remaining markers were subsequently incorporated into the map in the order of decreasing number of informative meioses using the ALL option. In many instances, the likelihood threshold had to be reduced to a LOD score of 2 in order to place these markers into the map due to a low number of informative meioses. The FLIPS option was used to evaluate local permutations of marker order. Finally, the CHROMPIC option was used to identify spurious double recombinants and to facilitate the correction of genotyping errors.

QTL analysis

Weights were collected from each of the bison herds over a 4-year period (1997–2000) using electronic scales. Weights were collected at approximately 6 (W6), 12 (W12) and 17 (W17) months of age corresponding to weaning, yearling and just prior to feedlot finishing. A total of 127 offspring (1998–2000) from both herds were used for weaning weight and 77 offspring for W17. Because HHP did not collect yearling weights, 97 offspring from the ABR herd (1997–2000) were used for the yearling weight analyses. For all QTL analyses, phenotypes were adjusted for age and gender.

The program LOKI v2.4.5 (Heath, 1997) was used to generate exact estimates of multipoint identity by decent (MIBD) values via MCMC analysis. Using the sex averaged linkage map generated from CRI-MAP, MIBD values were estimated at 1 cM intervals along each chromosome. An initial burn-in of 1,000 iterations was followed by 500,000 iterations where estimates were collected every 5th iterate.

Multipoint QTL analysis was also performed using LOKI, however, 2 million iterations were run after an initial burn-in of 10,000 iterates. A detailed description of the model and MCMC sampling process is described in Heath (1997). Briefly, the trait is modeled by k biallelic QTL where for QTL i, genotypes A_1A_1, A_1A_2, and A_2A_2 have effects a_i, d_i, and $-a_i$, respectively. The model for trait y can be expressed as:

$$y = \mu + X\beta + \sum_{i=1}^{k} Q_i\alpha_i + Zu + e$$

where μ is the overall trait mean, β is an ($m \times 1$) vector of fixed effects and covariates, α_i is a (2×1) vector of allele substitution effects for the i^{th} QTL, u is an ($n \times 1$; n animals each with a single observation) vector of random normally distributed additive residual polygene effects, e is an ($n \times 1$) vector of normally distributed residuals, k is the number of QTL in the model, and X ($n \times m$), Q_i ($n \times 2$) and Z ($n \times n$) are incidence matrices for the fixed, QTL and polygenic effects, respectively. LOKI offers the analytical advantage of allowing the number of QTL in the model to vary while simultaneously analyzing the entire genome.

Variance component interval mapping was also performed using the program SOLAR v2.0.4 (Almasy and Blangero 1998) according to the documentation accompanying the software. Multipoint interval analysis using the MIBD estimates obtained from LOKI was conducted at 1 cM intervals using the MULTIPOINT command.

Results

Mapping

A total of 358 microsatellite loci were genotyped. In order to decrease costs and the time required for genotyping, 83 PCR multiplexes were developed containing 349 loci for an average of 4.2 loci per PCR. Nine loci were individually amplified due to unusual annealing temperatures or because primers were not compatible for multiplexing. Because some of the multiplexes and all of the individually amplified loci could be co-loaded, it was possible to genotype all 358 loci using only 72 lanes per animal for an average of 5.0 loci per lane.

Table 1. Number of loci mapped to bison chromosomes along with the size (Kosambi cM) of the sex specific and sex averaged maps. Sex averaged values for the corresponding cattle chromosomes are provided for comparison (http://www.marc.usda.gov).

BBI	Number loci	Cattle	Bison		
		Sex average (cM)	Sex average (cM)	Male (cM)	Female (cM)
1	28	124.2	136	125.4	147.6
2	22	120.4	142.4	130.8	162.3
3	12	103.5	106.6	98.2	117.4
4	14	88.8	101.1	79.2	118.1
5	13	118.3	133.9	121.3	142.4
6	14	104.7	116.5	104.1	131.8
7	9	124.4	134.1	121.5	162.2
8	10	112.2	106.6	87.3	121
9	9	101.9	92.3	84.1	100.3
10	11	79.4	104.8	107.3	100.6
11	11	96.9	90.8	83.4	101.2
12	8	105.8	109	105.1	114.3
13	8	65.8	72.7	53	81.5
14	9	74.5	79.4	69.9	89.3
15	8	81.3	95.2	86.5	97
16	7	71.7	87.2	93.7	81.8
17	6	85.8	62.7	60.3	68.3
18	6	76.1	83.9	77.3	110.5
19	10	99.5	107.7	97.6	118.9
20	8	52.6	78.9	72.1	87.7
21	6	56.3	65.4	66.1	73.2
22	7	81.1	86.7	78.1	98.8
23	12	58	66.9	63.1	75
24	12	56.5	82.3	82.9	89.2
25	5	54	54.6	39.3	73.2
26	5	57.1	65.3	55.8	89.6
27	6	64.1	75.4	68.8	86
28	6	39.6	46.2	39.8	51.5
29	11	60.7	62.6	45.9	85.3
Total	292	2415	2647	2398	2976

Only one locus (ILSTS065) failed to produce a PCR product despite numerous attempts to optimize PCR conditions. Additionally, the only marker for which null alleles were detected was RM404 located on chromosome 25. Most of the remaining markers produced alleles near the expected size ranges in cattle, although several loci had allele size distributions that differed substantially from cattle. The average number of alleles per locus was 4.7 and the average observed heterozygosity per locus was 50.2%.

The ability to place markers in a linkage map is ultimately dependent on the number of informative meioses and the genetic distance between flanking loci. Although the bison herds used in this study were numerically small and were not designed for mapping, a total of 292 markers were integrated into an autosomal linkage map for bison. Because of difficulty inferring phase for some markers, only 65% of these loci could be ordered with LOD support >3. For these markers, marker order agreed with published marker order for cattle thus providing preliminary evidence for conservation of synteny across the autosomes. Of the 66 loci which could not be mapped, 27 were monomorphic, one would not amplify and 38 were biallelic and could not be mapped because in the majority of segregating families all individuals were heterozygous making it impossible to infer phase. The sex averaged bison map (2,647 Kosambi cM) was approximately 9% longer than the corresponding USDA MARC map, which covered 2,415 cM (Table 1). This small degree of map inflation was expected due to the low numbers of informative meioses and the relatively small number of scored loci. The female map (2,976 cM) was 11% longer than the male map (2,398 cM). Figures representing both the sex average and sex specific bison linkage maps are available from the authors upon request.

Table 2. Most likely position, LOD and Bayes Factor statistical support and proportion of variance explained for weight QTL identified by both SOLAR and LOKI.

Trait	BBI	SOLAR		LOKI			
		Position	LOD	Position	BF	V_{gQTL} [a]	V_{tQTL} [b]
W6	2	3	1.44	1	6.69	0.19	0.17
	7	56	1.44	32	5.05	0.22	0.20
	15	110	1.01	107	3.08	0.17	0.15
	24	82	1.11	67	19.50	0.33	0.30
W12	4	14	1.48	17	7.94	0.30	0.26
	14	27	1.32	32	5.73	0.31	0.23
	15	56	1.26	65	3.81	0.27	0.23
W17	8	22	1.52	37	3.25	0.16	0.16
	14	63	3.27	62	31.2	0.40	0.38
	25	33	1.23	45	3.93	0.25	0.24

[a] Proportion of the genetic variance due to the QTL.
[b] Proportion of the total variance due to the QTL.

QTL scan

SOLAR and LOKI generally yielded concordant results and indicated 10 putative QTLs on eight chromosomes (Table 2). The only chromosome to achieve a LOD score >3 was BBI14 for W17. Test statistic profiles for BBI14 and 15 which showed evidence for two QTL influencing two different weight traits are presented in Fig. 1. Test statistic profiles for the remaining chromosomes can be found in Supplementary Fig. 1 (www.karger.com/doi/10.1159/000075726).

Discussion

Markers

The development of this panel of multiplexed markers will be of benefit for genetic diversity and QTL mapping studies of domestic cattle and their wild relatives. Given the close relationship between bison and cattle and the results of Ward (2000), it was expected that virtually all of the cattle microsatellite loci would amplify in bison, however, the degree of variation and thus the informativeness of these markers in bison was unknown. Of the 358 genotyped loci only one marker consistently failed to amplify while 27 (7.5%) were monomorphic in these two bison herds. Since the animals comprising the ABR and HHP herds were acquired from various regions of the country they should contain the majority of the genetic variation found in plains bison (data not shown). However, it is likely that for some loci there are additional alleles present in bison that were not sampled in these herds.

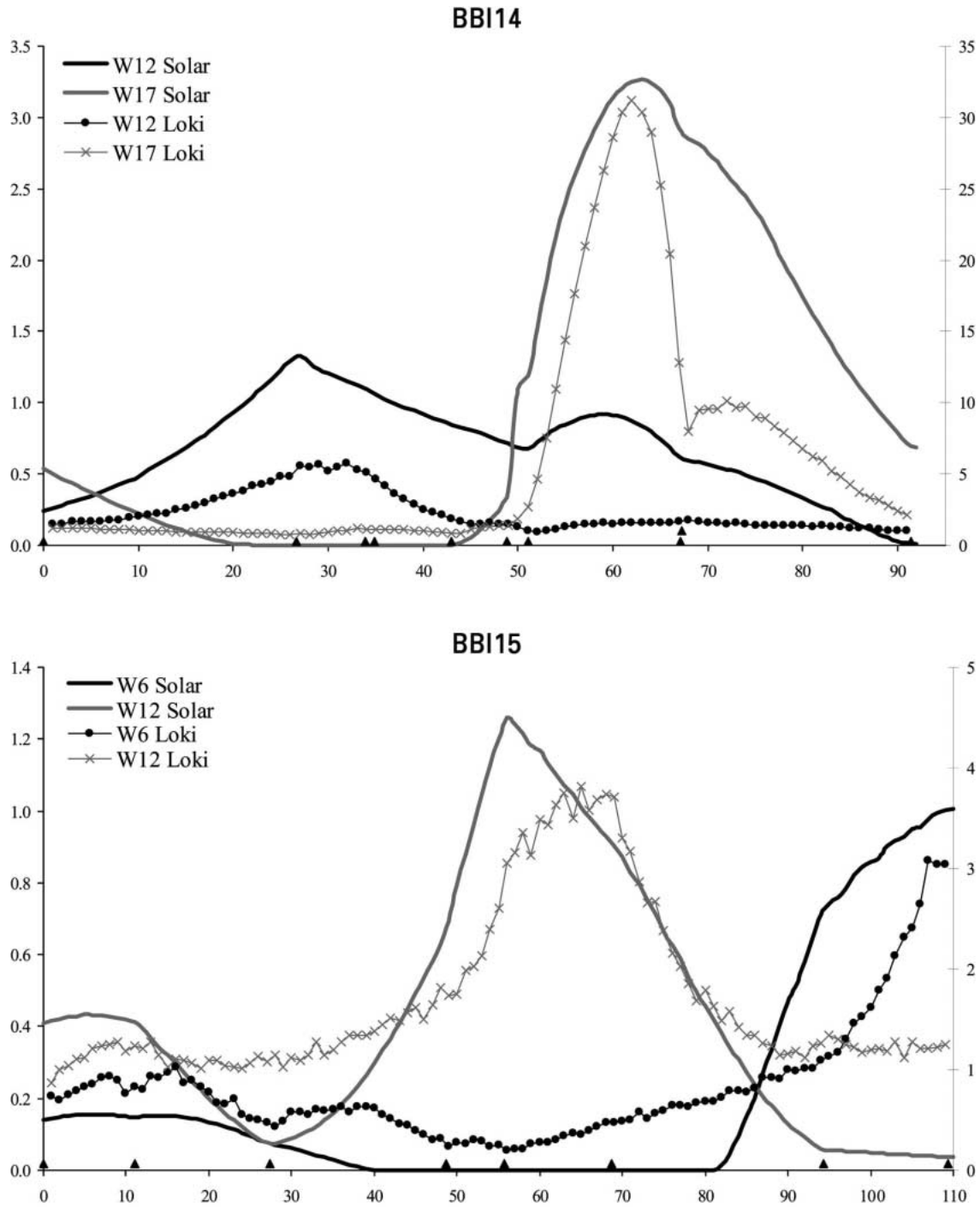

Fig. 1. Interval analyses of BBI14 and 15 using SOLAR and LOKI. All SOLAR results are relative to the left axis which is a LOD score. All LOKI results are relative to the right axis which is a Bayes Factor. Marker locations (Haldane cM) are indicated by triangles.

The average number of alleles in bison was 4.7 which is approximately half (9.3) the mean number of alleles for these same markers found in the USDA MARC mapping population which represents different cattle breeds from both *B. taurus* and *B. indicus*. However, bison compare favorably to the mean number of alleles of 4.5 for 20 microsatellites examined in 728 cattle from 20 populations as reported by MacHugh (1996). Thus, there is approximately the same level of allelic diversity when bison are compared to individual cattle breeds or populations but bison have half the number of alleles as compared to cattle in total.

The mean observed heterozygosity for the ABR and HHP herds was 50.2% (54.5% if monomorphic loci are excluded). This value is comparable to cattle in which Kappes et al. (1997) reported heterozygosities of 40.2% for linebred *B. taurus*, 42.5% for purebred *B. taurus*, and 59% for F_1 *B. taurus*. In addition, Grosz and MacNeil (2001) reported 57% heterozygosity for CGC dams and an F_1 bull and MacHugh (1996) reported a mean heterozygosity of 55.1% in a sample representing 20 populations from seven breeds. While bison may have lost some allelic diversity due to the population bottleneck of the latter part of the 1800's, they appear to have maintained at least as much heterozygosity as has been retained in the domestication and selective breeding of cattle. This is probably due to the short duration of the bottleneck and the manner in which the foundation herds were started with animals from diverse geographic areas which were subsequently used to populate private herds. The relatively high levels of heterozygosity, reflect only a limited degree of inbreeding and explain why bison have not experienced many of the complications associated with a severe bottleneck.

Mapping

Since the majority of the markers employed in this study have never been tested in bison, there was no prior information concerning their informativeness except for the results from cattle. Even though bison had half the number of alleles as cattle and the family size was far smaller than has previously been used in cattle mapping projects, a total of 292 loci (82%) were mapped. The sex averaged bison map (2,647 cM) was approximately 9% longer than the corresponding USDA MARC map, which spanned 2,415 cM (Table 1). Given the difference in the number of scored offspring and marker density, this map inflation was expected. As more offspring are genotyped (particularly with phase known meioses) and additional markers are added, it is expected that the Bison map will shrink and be very similar in length to the cattle map.

QTL Scan

The QTL scan identified eight chromosomes with similar statistical support for QTL using two different mapping approaches. Each of these chromosomes (except BBI14 for W17) failed to reach statistical support even for "suggestive" linkage as determined by Lander and Kruglyak (1995). However, the estimates of QTL location were generally in agreement between the two mapping approaches. In Table 1, the maximum LOD scores for these chromosomes are in the range of 1.0–1.5, which was approximately four times the average of the maximum LOD scores from the chromosomes without evidence for QTL (data not shown). We believe that the magnitude of the maximum LOD scores is due to the small family sizes rather than a lack of QTL segregating in bison.

Because bison and cattle are so closely related, it is useful to compare the results presented here with prior QTL reports from cattle. Half of the chromosomes found in this study have conserved synteny with regions harboring QTL in cattle. Kim et al. (2003) reported QTL on BTA2 affecting yearling, slaughter and hot carcass weight in the same region as the QTL on BBI2 affecting weaning weight. The most statistically significant QTL for 17-month weight on BBI14 is in the same region as a QTL affecting hot carcass weight in cattle (Kim et al., 2003). Casas et al. (2001) identified a QTL on BTA4 affecting hot carcass weight in the region corresponding to that harboring the yearling weight QTL on BBI4. Although the QTL on BTI8 identified by Casas et al. (2001) influenced fat depth, this QTL is in the same location as the yearling weight QTL identified in bison.

Polziehn et al. (1995) and Ward et al. (1999) identified the occurrence of bison in public herds carrying domestic cattle mitochondrial DNA, which is indicative of domestic cattle introgression during and following the bottleneck. In a study of introgressive hybridization between bison and cattle Ward (2000) identified 22 microsatellite markers, distributed across 12 autosomes, with differing allele size distributions between bison and cattle that can be used to distinguish bison and cattle alleles within these chromosomal regions. For these markers Ward (2000) identified domestic cattle alleles in five of the 14 public North American bison populations indicating nuclear as well as mitochondrial introgression. Four of the eight bison chromosomes putatively harboring growth QTL (BBI2, 4, 14 and 24) are included in the 12 chromosomes identified by Ward (2000). Most notably, the QTL on BBI14 affecting 17 month weight is flanked by species indicative markers BMS947 and BM4513, both of which showed no evidence for the introgression of domestic cattle alleles in the ABR or HHP herds. Although no hybrids were identified in these two herds for any of the chromosomes putatively harboring QTL, the possibility that the identified QTL were transferred laterally to bison from cattle cannot be excluded.

The fact that two species divergent by a million years possess similar QTL effects provides mutual support for the validity of these QTL. However, it remains open as to whether these QTL represent the same genes and if so, whether there were independent mutations in the *bison* and *bos* lineages, whether the same mutations have persisted following the original divergence or whether the bison QTL actually represent domestic cattle introgression. The latter issues might be addressed by fine mapping and examination of these regions for the presence of cattle haplotypes. If these were detected, bison may provide a useful resource for the positional cloning of these QTL based upon the minimal common cattle haplotype within hybrid bison.

The QTL identified on BBI7, 15, 24 and 25 do not have corresponding published QTL affecting weight reported in cattle. These QTL may not yet have been detected in cattle, may represent differences between bison and cattle, or they may be false positives. Due to the lack of power inherent to these pedigrees, this issue will not be resolved until additional offspring are added to the pedigrees or additional pedigrees are examined.

Conclusions

The development of the multiplex PCR protocols for this study represents, to our knowledge, the largest set of multiplexed microsatellite markers published to date for a livestock

species. These protocols should serve as the starting point for other laboratories wishing to optimize these loci based on other instrumentation and techniques. The cross-compatibility of most of the bovine markers enables markers to be multiplexed very easily and therefore should aid in the development of additional panels to address specific genome scan or diversity applications. The bison linkage map and marker data produced in this study should serve as the foundation for future mapping and population studies in bison. The population history of bison, their relationship to cattle and the fact that bison have only been under artificial selection for approximately 50 years offers a unique opportunity to study the genomes of two different but complementary species. The likelihood of positional cloning of QTL may be significantly enhanced if the same QTL appears to be segregating in different species.

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