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Identification of quantitative trait loci for milk yield in Murrah buffaloes

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ABSTRACT

A reference family consisting of 12 half sib sire families were created for the identification of QTLs for milk yield in buffaloes. Daughters were recorded for monthly test day milk yield. The number of daughters per sire varied from 50 to 335 daughters per sire. Seventy nine polymorphic microsatellite markers located on 8 chromosomes were genotyped for 2281 daughters of the 12 sires. Whole chromosome scanning was done using single marker analysis and interval mapping using three different algorithms. The analysis was carried out sire family wise. QTLs (63) were identified in single marker analysis and 32 QTLs were identified using interval mapping. The significance of LOD score was tested using permutation tests. The metaQTL analysis was carried out to find out the consensus chromosomal regions associated with milk yield in buffaloes. Five models were utilised and the best was selected on the basis of Akaike Information content. Total 23 chromosomal regions were identified for milk yield in buffaloes. 2 metaQTL chromosomal regions were identified on buffalo chromosome BBU2q; 3 metaQTLs each on buffalo chromosomes BBU8, BBU10 and BBU15 and 4 metaQTL regions each on BBU1q, BBU6, BBU9.

Key words: Buffaloes, MetaQTL analysis, Microsatellite, Milk yield, Quantitative trait loci (QTL), Reference family

Buffaloes contribute 49% to the total milk production in India (Basic Animal Husbandry and Fisheries Statistics 2017). Out of these, 35% is contributed by defined breeds and 14% by non descript buffaloes. Buffaloes have a long generation interval, value of each individual is high, limited female fertility (6–8 calves in lifetime) and almost all economic traits are expressed only in females (Sex limited) which makes buffalo an ideal species for application of Marker Assisted Selection. Weller (2001) reported MAS can potentially increase annual genetic gain by increasing the accuracy of evaluation, increasing the selection intensity and decreasing the generation interval. The information from genetic markers can be used to increase the accuracy of sire evaluations in addition to phenotypic information from daughter records (Meuwissen and van Arendonk 1992). Additionally, pre-selection of young sires for entry into the Progeny Testing (Kashi *et al.* 1990, Mackinnon and Georges 1998) can be done. Progeny test based on half-sib records and genetic markers can greatly enhance the accuracy of selection (Spelman *et al.* 1999). The use of genetic markers also reduce errors in parentage determination (Israel and Weller 2000). Meuwissen and van Arendonk (1992) reported that inclusion of marker information increases the accuracy of sire evaluations and increases the rate of genetic gain by 5% when the markers explained 25% of the genetic variance. The genetic gains of MAS do not wear out and are cumulative and eternal. Weller (1994, 2001) reported that investments in MAS are economically viable although the nominal costs are greater than the nominal gains.

The fundamental idea underlying QTL mapping is to associate the genotype and phenotype in a population exhibiting genetic variation. The identification of QTLs in buffaloes require large number of records for the traits of interest. It also requires information of pedigree and phenotypic records as well as the genotypes of the animals. Thus, identification of QTLs is a costly preposition. The buffalo is not a very well worked out species compared to cattle on several aspects. However, we have now sufficient information in buffaloes on its sequence and homology with cattle which can be utilised using comparative genomics. The draft sequence of buffalo is now available (Tantia *et al.* 2011), a great degree of concordance between buffalo and cattle has been established using radiation hybrid panel (Amaral *et al.* 2008). We utilised the information available in various cattle database for microsatellite selection for amplification in buffaloes. We targeted corresponding regions of 8 cattle chromosomes for identification of QTLs for milk yield in buffaloes (Fig. 1). The analysis was carried out utilising the data generated for 12 half sib families which were generated for the purpose and to increase the accuracy

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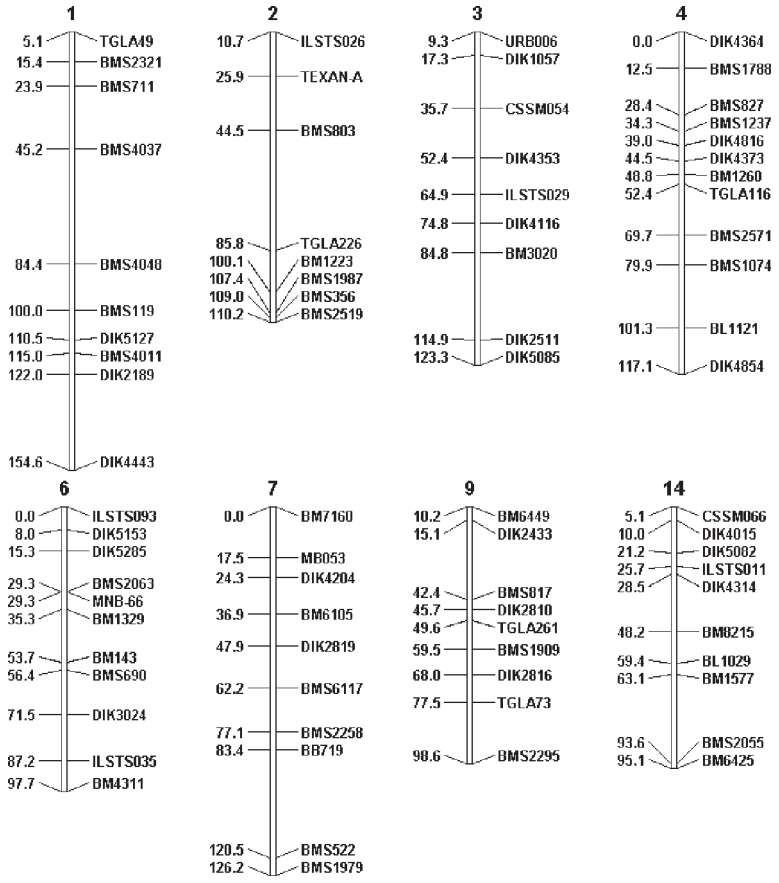

Fig. 1. Distribution of selected microsatellite markers along the 8 chromosomes of cattle equivalent chromosomes in buffaloes.

of data recording markers for paternity testing were reported (Vijh 2014). There has not been any report of identification of QTLs in buffaloes. The largest ever progeny testing program called associated herd progeny testing program currently being implemented provide 1st lactation records of only 8–10 daughters per sire (Annual reports of AICRP-Network Project 2013–14,15,16) which is not sufficient for the detection of QTLs for traits of economic importance. Thus this large experiment involving farmers was carried out to identify the markers (Chromosomal regions) responsible for milk yield and thus shall supplement the traditional selection procedures of sire evaluation. The QTLs in conjunction with traditional procedures shall enhance the accuracy of selection of the sires resulting in improvement in rate of genetic gain in buffalo species.

MATERIALS AND METHODS

The reference family of buffaloes (animals of known pedigree and having both genotype and phenotype information) was created for the work (Vijh *et al.* 2013). The accuracy of the records was authenticated using a set of DNA markers and only the daughters with confirmed paternity were recorded for phenotypes (Vijh *et al.* 2013). The daughters belonging to 12 half sib families were recorded for milk yield on monthly basis. The test day milk was recorded taking into consideration morning and evening milk. The total milk yield was estimated on the basis of the monthly test day records. The genotype data on 8 chromosomes of these animals was generated and has been reported (Vijh *et al.* 2013).

The single marker analysis of data was carried out using QTL cartographer software. For the identification of QTLs, the R/qtl software was utilised (Broman and Sen 2009). It has been implemented as an add-on package to the general statistical software R. The data generated fits into half sib design and the method used for the analysis of data was

Table 1. Sire wise distribution of daughters with first lactation milk records, mean, minimum and maximum milk yield of each sire family

Sire No.	No of daughters	Mean±SE (in kgs)	Minimum yield	Maximum yield
Sire1	319	1686.69±30.01	407.23	3615.85
Sire2	174	1629.81±35.21	483.00	3009.59
Sire3	99	1741.23±57.43	510.14	3368.53
Sire4	217	1658.90±32.92	520.69	3611.51
Sire5	273	1633.39±32.57	440.02	4093.00
Sire6	76	1820.97±62.49	428.02	3060.89
Sire7	335	1690.54±28.50	546.39	3611.51
Sire8	274	1654.67±33.20	430.04	4035.00
Sire9	224	1746.28±38.19	425.53	3935.16
Sire10	159	1712.06±38.11	706.69	3241.59
Sire11	81	1598.37±42.38	675.04	2588.00
Sire12	50	1736.89±77.01	601.92	3493.00

Table 2. List of significant QTL of milk yield for 12 half sib families using single marker analysis

Sire No.	Chromosome number (BTA)	Marker name	LOD	R^2	P (F value)
Sire1	4	BMS1237	4.701	0.0333	0.0316*
	4	DIK4373	7.105	0.0094	0.0082**
	6	DIK5153	4.709	0.0261	0.0314*
	7	MB053	4.952	0.0338	0.0273*
	9	TGLA261	5.258	0.0436	0.0230*
	14	BMS2055	4.332	0.0287	0.0390*
Sire2	2	BMS356	7.082	0.056	0.0088**
	3	DIK5085	7.302	0.0995	0.0078**
	7	BB719	9.696	0.1064	0.0022**
	9	DIK2433	4.149	0.0431	0.0449*
	9	DIK2810	6.712	0.1071	0.0107*
Sire3	1	BMS711	4.868	0.0841	0.0311*
	2	BMS1987	5.21	0.079	0.0257*
	3	DIK5085	4.458	0.0593	0.0391*
	4	DIK4364	4.948	0.088	0.0297*
	4	DIK4816	6.385	0.1349	0.0136*
	6	ILSTS093	8.297	0.0865	0.0049**
	6	MNB-66	5.345	0.0399	0.0239*
	14	BM6425	4.64	0.0927	0.0353*
Sire4	1	BMS4048	5.424	0.0455	0.0215*
	6	DIK3024	10.565	0.0656	0.0013**
	6	ILSTS035	5.186	0.0139	0.0246*
	7	DIK4204	4.66	0.0427	0.0331*
	7	DIK2819	4.147	0.0456	0.0444*
	7	BMS1979	4.759	0.0156	0.0313*
	9	DIK2810	7.785	0.0681	0.0059**
	9	TGLA261	8.671	0.0423	0.0037**
Sire5	2	TGLA226	7.637	0.0702	0.0063**
	3	URB006	3.934	0.0423	0.0497*
	4	BMS1237	4.518	0.048	0.0355*
Sire6	1	BMS711	6.309	0.1534	0.0152*
	2	BM1223	6.511	0.1584	0.0136*
	6	DIK5285	4.534	0.1125	0.0396*
	9	DIK2433	4.907	0.1041	0.0323*
Sire7	6	DIK5285	11.637	0.0423	0.0007***
	6	ILSTS035	5.77	0.0554	0.0172*
	7	BMS6117	5.192	0.0098	0.0238*
	7	BMS2258	4.735	0.0204	0.0309*
	14	BL1029	4.513	0.0198	0.0351*
Sire8	3	DIK1057	4.112	0.0316	0.0447*
	4	BMS1074	6.485	0.0543	0.0117*
	4	BL1121	4.136	0.0331	0.0440*
	6	BM4311	7.256	0.0571	0.0076**
	7	BMS6117	4.099	0.0041	0.0450*
	7	BB719	7.408	0.0356	0.0070**
Sire9	1	BMS2321	4.928	0.0413	0.0287*
	1	BMS711	4.183	0.0454	0.0438*
	6	BM143	4.575	0.0256	0.0350*
	6	BMS690	6.045	0.038	0.0154*
	7	BMS1979	4.28	0.0375	0.0414*
	9	BMS817	4.496	0.0328	0.0366*
Sire10	1	TGLA49	5.746	0.0683	0.0190*
	4	BMS1788	4.245	0.0722	0.0438*
Sire11	3	CSSM054	5.863	0.4006	0.0280*
	6	BM143	5.995	0.2914	0.0263*
	6	DIK3024	5.197	0.1991	0.0386*
	14	BM8215	5.142	0.3703	0.0396*
	14	BM1577	6.835	0.2788	0.0177*
Sire12	1	BMS4048	6.97	0.1193	0.0142*
	1	BMS119	7.499	0.2973	0.0110*
	1	DIK2189	4.689	0.2168	0.0444*
	6	BM143	7.114	0.2162	0.0132*
	9	DIK2810	5.986	0.3904	0.0231*

Signif. codes: ***0.001, **0.01, *0.05.

backcross which is the simplest possible experimental cross. The QTL data was prepared as per the requirement of the software, i.e. three interrelated data structures: the phenotypes, the genotypes and the marker map. Thus, total 12 data set were created and analysis was carried out family wise. For a single QTL model, we utilised the standard interval mapping which uses maximum likelihood estimation under a mixture model, the other algorithm Haley-Knott regression methods use approximations to the mixture model. The third method utilised was multiple imputation which uses the same mixture model but with multiple imputation in place of maximum likelihood. The LOD score indicated the evidence for the presence of a QTL, with larger LOD scores corresponding to greater evidence. We utilised the permutation test (Churchill and Doerge 1994) with 1000 replicates and calculated p -value as the proportion that meet or exceed a particular observed LOD score. The multiple QTL models as implemented in R/qtl were used as they have increased power to detect QTL, better separation of linked QTLs and defining epistatic interactions. We fitted the Full QTL model using the *fitqtl* function of R/qtl package and this also included the interaction among the QTLs. The ANOVA table indicates the overall fit of the model; the LOD score obtained is relative to the null model (with no QTL). The drop one QTL model was utilised to see the effect of each QTL and its related interactions and thus provides support for the individual terms in the model. The effect of each QTL was also estimated.

QTL meta-analysis was utilised to synthesize QTL information from 12 independent half sib family analysis and to refine the chromosomal region involved in trait variation control as implemented in Biomercator software. The QTL meta-analysis algorithm developed by Goffinet and Gerber (2000) was used. We fitted five models, the most likely QTL arrangement, assuming a Gaussian distribution, was determined by means of the maximum likelihood method and an Akaike-type statistical criterion

Table 3. List of significant QTL locations for 12 half sib families using interval mapping (Haley-Knott regression and extended Haley-Knott regression) method of R/qtl

	Chr	Pos	LOD	R^2 or % variance	F value	P value (F)	Significance
Sire1	4	20	1.18	1.58	2.6094	0.0752	P
	7	20	1.17	1.56	2.5642	0.0787	P
Sire2	1	89.1	3.61	8.2678	2.6268	0.0187	*
	1	55.1	1.58	3.5684	3.3521	0.035	*
	2	100.8	3.665	8.3889	2.6653	0.0172	*
	1@89.1:2@100.8		2.5650	5.7852	2.7571	0.0298	*
Sire4	1	55.1	3.077	5.95	2.294	0.0364	*
	9	50.2	2.9261	5.65	2.178	0.0465	*
	1	105.1	3.317	6.1748	2.4067	0.0288	*
	4	24	3.5472	6.62	2.5801	0.0198	*
	14	59.4	1.984	3.64	4.2573	0.0155	*
	1@105.1:4@24.0		2.9098	5.3932	3.1531	0.0153	*
Sire5	1	19.1	1.2794	1.8941	2.7488	0.0659	P
	3	103.3	1.2391	1.8339	2.6613	0.0718	P
	7	10	2.7749	4.1608	2.0127	0.0645	P
	7	44	4.2075	6.37	3.0893	0.00617	**
	14	89.1	3.5811	5.39	2.6154	0.01775	*
	7@44.0:14@89.1		2.9254	4.3811	3.1869	0.01409	*
Sire6	3	33.3	1.3579	6.28	2.616	0.0813	P
Sire7	4	50	1.144	1.39	2.4567	0.0874	P
Sire8	7	94	1.2135	1.8598	2.6065	0.0758	P
	4	80	3.21	4.95	2.3770	0.0298	*
	1	35	1.256	1.9031	2.7422	0.0663	P
Sire9	1	15.1	1.2775	2.3979	2.7810	0.0643	P
	14	35.1	1.2505	2.3465	2.7214	0.0681	P
Sire10	1	105.1	1.2591	2.921	2.6370	0.0751	P
	2	20.8	1.9768	4.63	4.1836	0.0172	*
	4	60	1.1512	2.6664	2.4072	0.0937	P
Sire11	3	29.3	1.547	5.688	2.75863	0.0714	P
	1	9.1	1.666	5.75	2.981	0.0583	P
	9	60.2	4.4141	16.514	2.853	0.0164	*
	14	35.1	3.8086	13.996	2.418	0.0369	*
	9@60.2:14@35.1		2.8956	10.360	2.684	0.0398	*
Sire12	3	23.3	3.4574	21.94	2.187	0.0677	P
	9	70.2	3.3261	20.972	2.091	0.0793	P
	3	9.3	4.748	23.71	3.0172	0.0183	*

Signif. codes: ***0.001, **0.01, *0.05. P, Probable QTL.

Table 4. Locations of metaQTL regions (chromosome wise) along with their confidence interval.

BTA Chr	BBU Chr	AIC value	Mean position 0 (C.I.)	Mean position 1 (C.I.)	Mean position 2 (C.I.)	Mean position 3 (C.I.)
1	BBU1q	117.7	14.41 (12.4 - 16.41)	33.04 (28.8 - 37.28)	83.34 (79.28 - 87.41)	105.31 (102.84 - 107.78)
2	BBU2q	9.54	20.77 (15.77 - 25.97)	100.17 (95.77 - 102.77)	-	-
3	BBU6	32.1	12.34 (9.34 - 16.34)	23.34 (19.34 - 31.34)	31.63 (27.84 - 35.41)	99.34 (96.34 - 102.34)
4	BBU8	34.57	21.13 (16.22 - 26.05)	49.76 (47.27 - 52.26)	79.92 (77.0 - 85.0)	-
7	BBU9	26.01	12.0 (8.0 - 15.0)	18.0 (11.0 - 21.0)	42.0 (38.0 - 46.0)	95.0 (85.0 - 100.0)
9	BBU10	15.61	48.2 (45.2 - 51.2)	59.51 (56.2 - 64.2)	68.07 (64.2 - 71.2)	-
14	BBU15	24.89	39.23 (35.4 - 43.05)	48.22 (42.12 - 52.12)	58.12 (52.12 - 61.12)	-

indicated the best model amongst the five. For this model, consensus QTL positions were determined as the mean of QTL distribution maximizing the likelihood.

RESULTS AND DISCUSSION

The milk yield in buffaloes is the most important economic trait. The milk yield is a quantitative trait and follows a near normal distribution, and controlled by large number of genes. The study of the genotype based on molecular markers (microsatellites) and the phenotype data and their associations can help determine the number and nature of QTLs controlling the milk yield. To detect the association between microsatellites and milk yield, we can use data analysis approaches which include the single marker

analysis as well as interval mapping. As the milk yield was recorded on daughters of 12 sires, the analysis was also carried out family wise. The number of daughters recorded for each sire, the mean, minimum and maximum milk yield during the first lactation has been given in Table 1.

The single marker analysis have several advantages as it is simple to detect, does not require very complicated models/software, more so it does not require the linkage map (Collard *et al.* 2005). In the half sib family analysis or a backcross, we test for linkage of a marker to a QTL and the evidence of linkage is measured by a LOD score which is the likelihood ratio comparing the hypothesis that there is a QTL at the marker to the hypothesis that there is no QTL anywhere in the genome. The analysis of 12 half sib families and the markers which were found significant, level of significance, LOD score and R^2 is given in Table 2.

The different markers have been identified in different families (Half sib) and this can be attributed to heterozygosity of the sire at tested loci. All the sires may not be heterozygous for all the loci and the QTLs can only be identified in markers which are heterozygous in sires and thus segregating. However, the primary disadvantage of the single marker analysis is need to omit the individuals with missing marker information. Such was not a case in our analysis. However, the other notable shortcoming is that one cannot inspect the position between the markers and one receives only a poor information about the position of QTLs. We thus applied the interval mapping and Multiple QTL models for analysis.

The interval mapping as implemented in R/qtl was carried out using the Haley-Knott regression and extended Haley-Knott regression method to fit the multiple QTL model. The identified QTLs in the 12 sire families with position, chromosome no., LOD score, percentage of variance, F value and significance is given in Table 3 and representative chromosomal scans have been depicted as Fig. 2 (a to d). Significant interactions among BTA1 and BTA2 at position 89.1 and 100.8, BTA1 and BTA4 at positions 105.1 and 24, BTA7 and BTA14 at positions 44 and 89.1, and BTA9 and BTA14 at positions 60.2 and 35.1 were observed.

The metaQTL analysis to define the consensus QTLs have been summarised in Table 4. The selection of the model from the 5 models tested for the analysis was carried out on the basis of Akaike Information Content like statistics. The model and the metaQTL regions were selected on the basis of AIC values. The chromosome number, MetaQTL location along with their confidence interval are given in Table 4. The metaQTL positions for the 7 chromosomes (as BTA6 equivalent buffalo chromosome did not reveal any QTL for milk yield in buffaloes) are shown in Fig. 3. The chromosome 1 (BTA 1/BBU1q) had 4 metaQTL positions. The locations of QTLs were at chromosomal location 12.4–16.41, 28.8–37.28, 79.28–87.41 and 102.84–107.78 cM. The QTLs on these locations have also been reported in cattle (Nadesalingam *et al.* 2001, Michenet *et al.* 2016 and Viitala *et al.* 2003). On the second chromosome

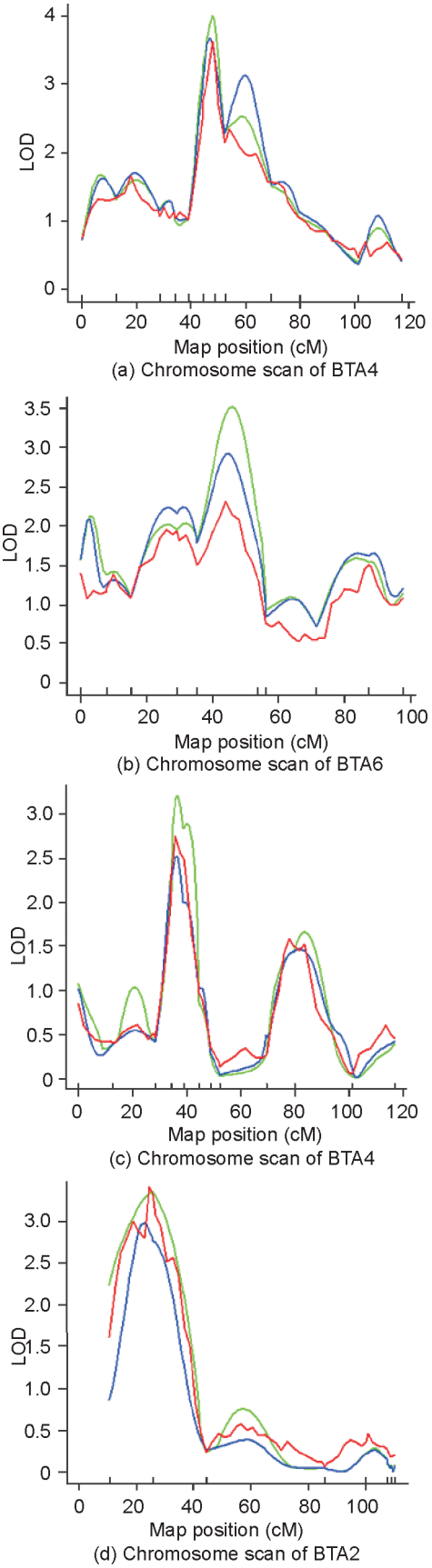

Fig. 2. Representative chromosome scans showing probable QTLs identified on the basis of high LODs for different half sib families.

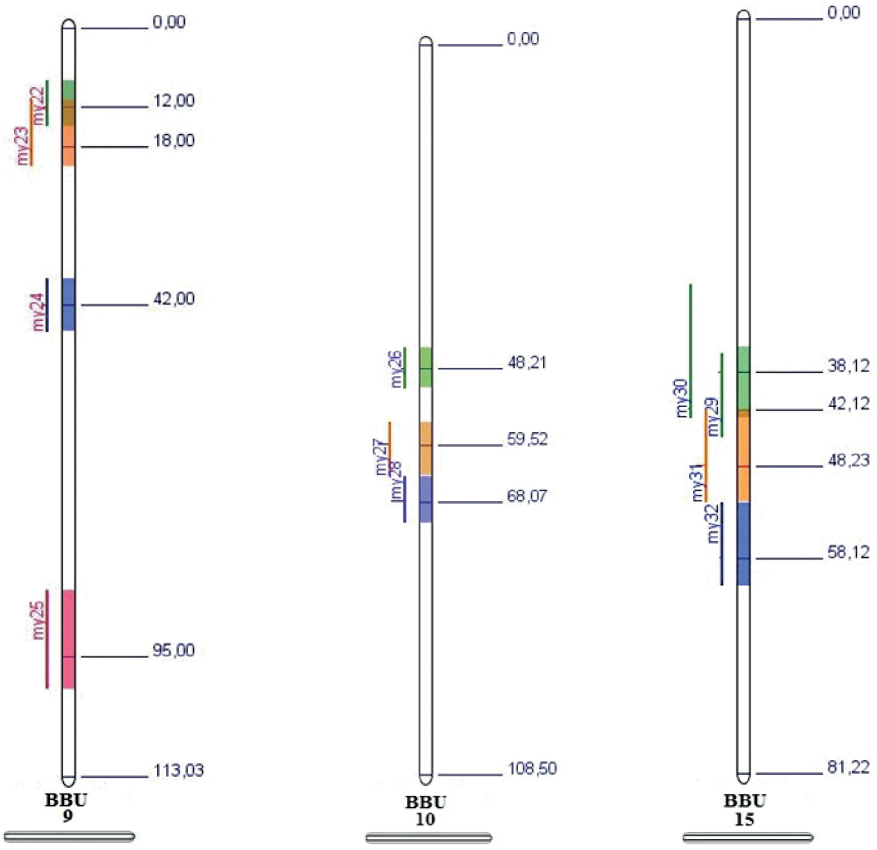

Fig. 3. The metaQTL positions on 7 chromosomes for buffalo.

(BTA2/BBU2q), 2 metaQTL locations were identified between 15.77–25.97 and 95.77–102.77 cM. Several authors have also reported QTLs in cattle on these locations (Doran *et al.* 2014, Vitala *et al.* 2003 and Cole *et al.* 2011). The buffalo chromosome BBU6 (BTA3) also revealed 4 metaQTL locations between 9.34–16.34, 19.34-31.34, 27.84–35.41 and 96.34–102.34 cM. QTLs have also been reported on these chromosome locations by several authors in cattle (Doran *et al.* 2014, Vitala *et al.* 2003, Daetwlar *et al.* 2008, Rodreiguez-zas *et al.* 2002, Michenet *et al.* 2016 and Bagneto *et al.* 2008). The buffalo chromosome BBU8 (BTA4) revealed 3 metaQTLs regions spanning 16.22–26.05, 47.27–52.26 and 77.00–85.0 cM. Few reports of the presence of QTLs in these regions in several breeds of cattle have been reported (Michenet *et al.* 2016, Bagnato *et al.* 2008, Rincon *et al.* 2009 and Cole *et al.* 2011). The buffalo chromosome BBU9 (BTA7) revealed 4 metaQTL regions as given in Table 4. There are reports of the same regions harbouring QTLs in cattle (Cole *et al.* 2011, Schrooten *et al.* 2004, Michenet *et al.* 2016 and Nayeri *et al.* 2016). Similarly, the buffalo chromosome 10 and 15 (BTA 9 and BTA 14) revealed metaQTL locations at 3 locations on each of the chromosomes. The regions have also been associated with QTLs of milk yield in cattle (Nayeri *et al.* 2016, Vilkki *et al.* 1997, Cole *et al.* 2011, Plante *et al.* 2001) for chromosome BTA 9 and for chromosome no. 14 (Meredith *et al.* 2012).

Thus we identified 23 chromosomal regions on 7 chromosomes which associated with milk yield in buffaloes. The eighth chromosome BTA6 did not reveal any QTL using the chromosomal scans. We utilised the microsatellites from the cattle database and the locations as reported in the database. The chromosomal homology between cattle and buffalo has been delineated using radiation hybrid panels (Amaral *et al.* 2008). There are usually large number of genes underlying the chromosomal region and can be identified using comparative genomics.

The QTL regions of the chromosomes segregate along the family lines and suffer from this disadvantage that they cannot be used across families. Their usage in the families can greatly enhance the accuracy of selection and resultant genetic gain per year. This is the first report of the identification of QTLs for milk yield in buffaloes and has been filed for grant of patent vide application no. 1889/DEL/2013 dated 26 June, 2013.

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