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Linkage Disequilibrium and Haplotype Block Structure in Portuguese Holstein Cattle

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ABSTRACT

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The objectives of this study were to estimate linkage disequilibrium (LD), describe and scan a haplotype block for the presence of genes that may affect milk production traits in Portuguese Holstein cattle. Totally 526 animals were genotyped using the Illumina BovineSNP50 BeadChip, which contained a total of 52 890 single nucleotide polymorphisms (SNPs). The final set of markers remaining after considering quality control standards consisted of 37 031 SNPs located on 29 autosomes. The LD parameters historical recombinations through allelic association (D') and squared correlation coefficient between locus alleles frequencies (r^2) were estimated and haplotype block analyses were performed using the Haploview software. The averages of D' and r^2 values were 0.628 and 0.122, respectively. The LD value decreased with increasing physical distance. The D' and r^2 values decreased respectively from 0.815 and 0.283 at the distance of 0–30 kb to 0.578 and 0.090 at the distance of 401–500 kb. The identified total number of blocks was 969 and consisted of 4259 SNPs that covered 159.06 Mb (6.24% of the total genome) on 29 autosomes. Several genes inside the haplotype blocks were detected; *CSN1S2* gene in haplotype block 51 on BTA 6, *IL6* and *B4GALT1* genes in haplotype blocks 6 and 33 on BTA 8, *IL1B* and *ID2* genes in haplotype blocks 19 and 29 on BTA 11, and *DGAT1* gene in haplotype block 1 on BTA 14. The extension of LD using BovineSNP50 BeadChip did not exceed 500 kb and its parameters r^2 and D' were less than 0.2 and 0.70, respectively, after 70–100 kb. Consequently, the 50K BeadChip would have a poor power in genome wide association studies at distances between adjacent markers lower than 70 kb.

Keywords: single nucleotide polymorphism; GWAS; dairy cattle

Linkage disequilibrium (LD) has been defined as the non-random association between alleles at different loci (Phillips et al. 2003; Khatkar et al. 2006b, 2008; Odani et al. 2006). Information concerning the structure of LD at the population level is crucial for interpretation and application of the results of genome wide association studies (Meuwissen and Goddard 2000; Khatkar et al. 2006a; Bohmanova et al. 2010; Lu et al. 2012) and for determination of the statistical

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power of association studies (Khatkar et al. 2007; Kim and Kirkpatrick 2009). Characterization of the empirical patterns of LD across the genome is important to improve our understanding the biological pathway of recombinations and selection results in the bovine genome (Khatkar et al. 2006a; Bohmanova et al. 2010). Furthermore, understanding the genomic landscape of bovine LD and variation in recombination rates facilitates the efficient design and analysis of association studies and greatly improves inferences from DNA marker polymorphism data based on population studies (Khatkar et al. 2006b). The construction of a high-resolution LD map for the bovine genome will provide further insights into the effects of selection and evolutionary forces upon the genomes of breeds which have been selected for different agricultural purposes (McKay et al. 2007). There are different measures of LD such as D' and r^2, D' estimates historical recombinations through allelic association, whereas r^2 measures the squared correlation coefficient between locus alleles frequencies (McKay et al. 2007; Bohmanova et al. 2010). The range of either of these measures extends between 0 and 1. D' < 1 indicates that historical recombinations have occurred between the loci, and D' = 1 indicates absence of recombination between the two loci because of the occurrence of one of the polymorphisms. Therefore, D' is rather an indicator of missing haplotypes than being a reliable measure of LD. Moreover, D' tends to be strongly inflated for small samples and in the presence of a rare allele. The r^2 value represents the degree of association between the two loci, it equals 1 only if two haplotypes are present, which is usually a consequence of population bottlenecks or genetic drift. Dealing with the r^2 value is preferred for association studies, because there is a simple inverse relationship existing between r^2 and the sample size that is required to detect the association between QTL and SNP (Bohmanova et al. 2010).

Haplotype blocks are chromosome regions that show high LD, low haplotype diversity, and low recombination rate (Phillips et al. 2003; Khatkar et al. 2007). They are inherited from one generation to another as single units (Lin and Zhao 2010), and may arise by several factors such as recombinations, selection, population bottlenecks, population admixture, and mutations (Phillips et al. 2003; Guryev et al. 2006). Haplotypes can describe genetic variation and LD patterns in cattle genome and proved to be more powerful than single-marker methods in association studies (Lin and Zhao 2010). It is important to construct the haplotype blocks and identify genes involved in them in farm animals, especially those having effects on the important economic traits, such haplotype block should be scanned for deleterious gene effects before incorporation into selection programs.

There is a tremendous interest to study LD and patterns of haplotype blocks in domestic animals. Khatkar et al. (2006a) constructed a haplotype block for 433 Australian dairy bulls using 220 single nucleotide polymorphisms (SNPs) on BTA 6 and found 40 blocks occupying 41% of the chromosome. Kim and Kirkpatrick (2009) identified 128 haplotype blocks across the genome of 200 North American Holstein cows using 7119 SNPs. Khatkar et al. (2007) identified 727 blocks in 1000 Holstein Friesian bulls using 15 036 SNPs.

The objectives of this work were to estimate linkage disequilibrium and describe haplotype block structure for Portuguese dairy cattle, and to scan the identified haplotype block for the presence of genes that may affect milk production traits.

MATERIAL AND METHODS

A total of 526 animals were genotyped using the Illumina BovineSNP50 BeadChip, which contained a total of 52 890 SNPs (Illumina, USA). Animals with more than 20% missing marker genotypes were excluded from the analysis. A SNP was removed from the analysis if it had minor allele frequency (MAF) less than 2%, call rate less than 90% or exhibited deviation from Hardy–Weinberg equilibrium (HWE) with $P < 10^{-6}$. Filtration of the marker data was performed using Plink software (Purcell et al. 2007). After the SNP data filtration, the final marker set remaining for analysis was 37 031 SNPs from 29 autosomes. The missing genotypes were imputed using Beagle software (Browning and Browning 2009). The LD parameters D' and r^2 were estimated and haplotype block analyses were performed using the Haploview software (Barrett et al. 2005). To study the decline of LD, the physical distances between markers were classified into seven intervals: < 30 kb, 31–70 kb, 71 to 100 kb, 101–200 kb, 201–300 kb, 301–400 kb, and 401–500 kb. The Genome Bos_Taurus_UMD_3.1 in the NCBI database was used to determine the

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location of genes affecting milk production and mastitis traits as reported by Ogorevc et al. (2009), and all identified haplotype blocks were scanned to determine the genes located inside them.

RESULTS AND DISCUSSION

The BTA length, SNPs number, interval between markers, observed heterozygosity, predicted heterozygosity, and MAF are presented in Table 1. The average marker interval, observed heterozygosity, predicted heterozygosity, and MAF for SNPs used in this study were 67.80, 0.365, 0.352, and 0.264 kb, respectively. The minimum average marker interval was 60.62 kb on BTA 25, and the maximum was 79.70 kb on BTA 5. The highest number of SNPs on the chromosomes was 2499 on BTA 1, and the lowest was 679 on BTA 28. Also, the highest MAF value was 0.280 on BTA 18, and the lowest was 0.255 on BTA 1. The value of MAF affects the distribution and extent of LD (Khatkar

Table 1. Chromosome length, number of single nucleotide polymorphisms (SNPs), marker interval, heterozygosity, and minor allele frequency (MAF) for 29 autosomes in Portuguese Holstein cattle

BTA	BTA length (Mb)	SNPs (*n*)	Marker interval (kb)	Hetero-zygosity	MAF
1	161.11	2 499	64 406	0.3444	0.255
2	140.80	1 944	70 323	0.3579	0.266
3	127.92	1 791	69 976	0.362	0.270
4	124.45	1 829	65 687	0.358	0.263
5	125.85	1 564	79 709	0.3529	0.266
6	122.56	1 903	62 573	0.3546	0.265
7	112.08	1 578	71 264	0.3443	0.258
8	116.94	1 717	67 327	0.351	0.256
9	108.15	1 501	69 995	0.3451	0.259
10	106.38	1 545	67 469	0.3593	0.264
11	110.17	1 597	67 154	0.3548	0.262
12	85.36	1 229	74 059	0.3605	0.265
13	84.42	1 262	66 308	0.361	0.271
14	81.35	1 323	62 899	0.366	0.280
15	84.63	1 225	68 435	0.3575	0.226
16	77.91	1 149	70 774	0.3594	0.264
17	76.51	1 134	66 096	0.3562	0.263
18	66.14	938	69 426	0.37101	0.280
19	65.31	971	65 506	0.3715	0.273
20	75.80	1 127	63 942	0.3605	0.259
21	69.17	1 015	70 116	0.3501	0.267
22	61.85	898	68 245	0.3495	0.262
23	53.38	771	67 824	0.3598	0.267
24	65.02	899	69 900	0.349	0.262
25	44.06	714	60 626	0.3609	0.279
26	51.75	771	66 173	0.3332	0.252
27	48.75	699	64 946	0.3474	0.262
28	46.08	679	67 882	0.3673	0.271
29	52.00	759	67 417	0.3656	0.272

Table 2. Average and median of historical recombinations through allelic association (D') and squared correlation coefficient between locus alleles frequencies (r^2) of linkage disequilibrium for Portuguese dairy cattle

BTA	BTA length (Mb)	D'		r^2	
		mean	median	mean	median
1	161.11	0.657	0.744	0.137	0.057
2	140.80	0.648	0.718	0.137	0.064
3	127.92	0.646	0.72	0.130	0.06
4	124.45	0.626	0.677	0.119	0.051
5	125.85	0.627	0.678	0.121	0.052
6	122.56	0.628	0.679	0.127	0.056
7	112.08	0.660	0.753	0.141	0.061
8	116.94	0.663	0.7615	0.137	0.058
9	108.15	0.636	0.697	0.118	0.051
10	106.38	0.639	0.698	0.134	0.062
11	110.17	0.619	0.657	0.116	0.052
12	85.36	0.630	0.688	0.115	0.053
13	84.42	0.650	0.725	0.141	0.069
14	81.35	0.657	0.741	0.158	0.076
15	84.63	0.613	0.653	0.107	0.05
16	77.91	0.662	0.759	0.140	0.064
17	76.51	0.643	0.709	0.120	0.054
18	66.14	0.563	0.545	0.102	0.045
19	65.31	0.621	0.682	0.110	0.052
20	75.80	0.664	0.758	0.141	0.0635
21	69.17	0.616	0.662	0.121	0.054
22	61.85	0.632	0.687	0.117	0.051
23	53.38	0.628	0.677	0.115	0.055
24	65.02	0.611	0.641	0.120	0.053
25	44.06	0.579	0.586	0.110	0.055
26	51.75	0.632	0.695	0.119	0.047
27	48.75	0.581	0.577	0.088	0.039
28	46.08	0.578	0.576	0.098	0.046
29	52.00	0.614	0.648	0.104	0.049
Mean	87.79	0.628	0.682	0.122	0.055

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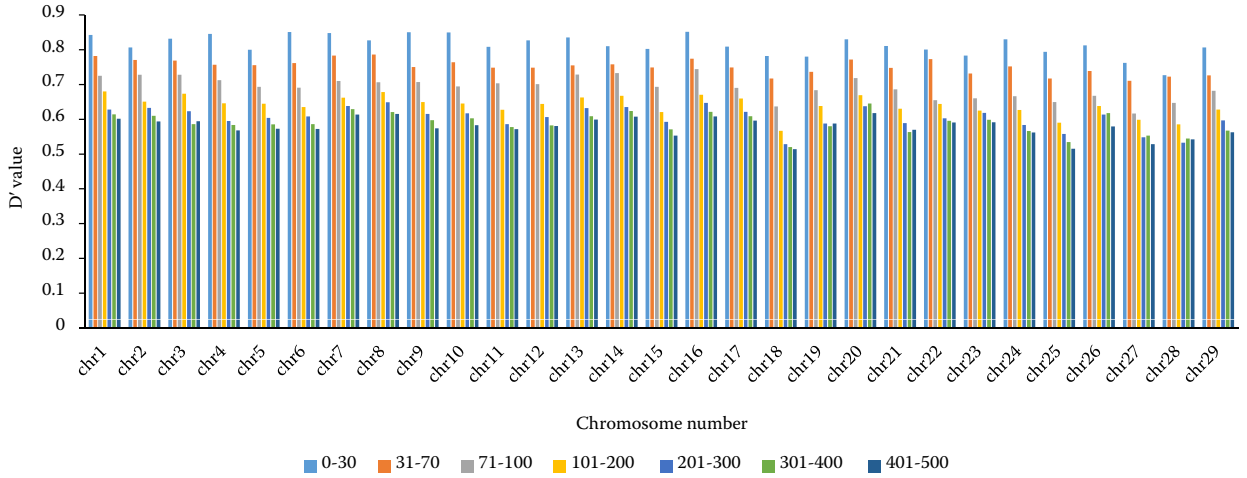

Figure 1. Averages of the historical recombinations through allelic association (D') parameter of linkage disequilibrium in different marker intervals of Portuguese Holstein cattle

et al. 2008). In the present study the distribution of MAF of SNPs was nearly uniform for all autosomes. Therefore MAF values had no effects on the distribution or extent of LD. These results are in agreement with those obtained on the SNPs of Illumina BovineSNP50K BeadChip for Holstein based on the Bovine Hapmap Consortium (2009). Other literature, however, reported higher MAF values than those in the present study (Bohmanova et al. 2010; Qanbari et al. 2010).

The D' and r^2 parameters of LD were estimated for pair-wise combinations of SNPs on each chromosome. The mean and median values of D' and r^2 for each chromosome are presented in Table 2. The averages of D' and r^2 values were 0.682 and 0.122, respectively. The highest D' value (0.664) was found on BTA 20 and the lowest (0.563) on BTA 18 (Figure 1). Also, the highest r^2 value (0.158) was found on BTA 14 and the lowest (0.098) on BTA 28 (Figure 2). Two theories to explain the difference in LD values on different chromosomes were set. The first, selection for production traits lasting for 50 generations or more results in QTL distribution throughout the genome and consequently generates different patterns of LD on each individual chromosome. The second, some chromosomes have higher rates of recombination causing lower LD than others (McKay et al. 2007).

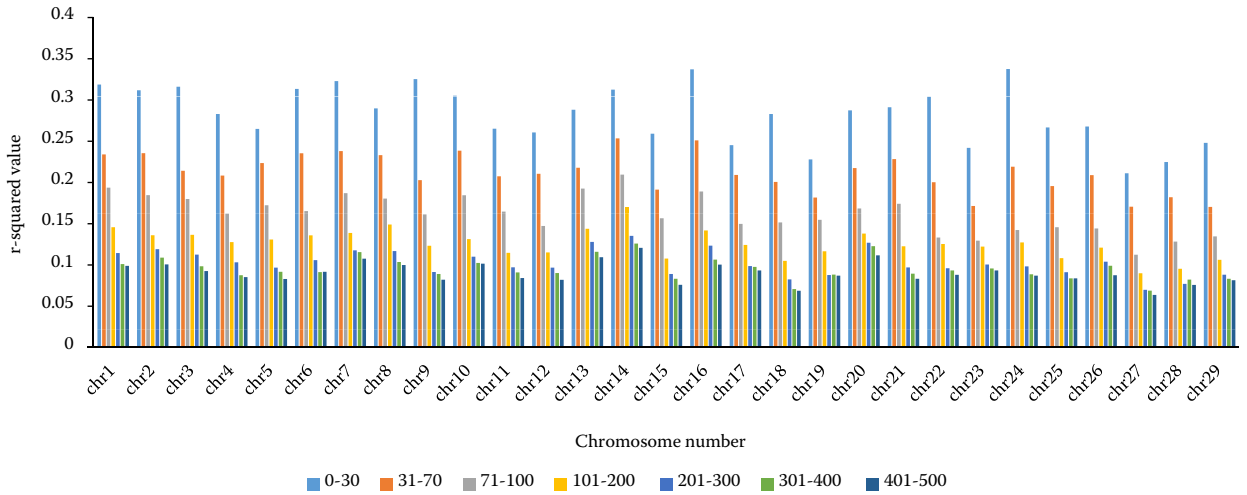

Figure 2. Averages of the squared correlation coefficient (r^2) parameter of linkage disequilibrium in different marker intervals of Portuguese Holstein cattle

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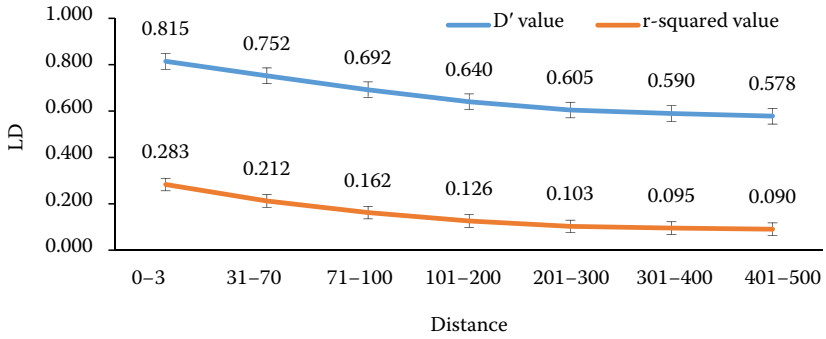

Figure 3. Overall means of linkage disequilibrium (LD) in different marker intervals

The high LD obtained on BTA 14 was expected since this autosome is known to carry genes affecting milk traits similar to *DGAT1* gene. Therefore, selection to improve milk traits would increase LD on BTA 14. In contrast, Lu et al. (2012) reported higher LD on BTA 5 in Angus beef cattle, because several QTLs and genes like *IGF-1* and *myf5*, which affect birth weight and carcass traits, were found on it. However, comparisons between LD values estimated in previous studies showed differences depending on marker type, sample size, and density. Therefore it was suggested that results should be compared at the same SNPs densities. Banos and Coffey (2010) evaluated LD in two divergent lines (133 control and 166 selected Holstein cows) using 41 859 SNPs and estimated r^2 values of 0.069 and 0.071, respectively. These estimates were smaller than those found in the present study probably due to the high intensity of selection.

In the current study the decline in LD was measured by classifying LD into seven intervals. The values of D' and r^2 decreased with the increase of the physical distance (Figure 3). The value of D' decreased from 0.815 at the distance of 0–30 kb to 0.752 at the distance of 30–70 kb to reach 0.578 at 401–500 kb. The same trend was noted for r^2 values which decreased from 0.283 at the distance of 0–30 kb to 0.213 at 30–70 kb and finally to 0.090 at the distance of 401–500 kb. Nevertheless, the values of r^2 were > 3 at the distance of 0–30 kb for chromosomes 6, 7, 9, 10, 14, 16, 22, and 24 (Supplementary Tables S1 and S2 in Supplementary Online Material (SOM)). These results are in agreement with those of previous studies (Bohmanova et al. 2010; Qanbari et al. 2010; Espigolan et al. 2013). In addition, the current study confirmed that the extent of LD available for the association analysis in Portuguese Holstein population does not significantly exceed 500 kb. Meuwissen et al. (2001) suggested that r^2 of 0.2 is required in genomic selection to achieve an accuracy of 0.85 for genomic breeding values. Qanbari et al. (2010) suggested that the convenient value of r^2 for association studies was 0.25. O'Brien et al. (2014) showed that r^2 values above 0.3 were required to give sufficient power in genome wide association studies (GWAS). In the current study, r^2 values above 0.2 were achieved at a distance less than 70 kb between adjacent markers, indicating that using BovineSNP50K BeadChip with marker interval 67.8 kb is inconsistent for achieving a high accuracy of genomic breeding values and

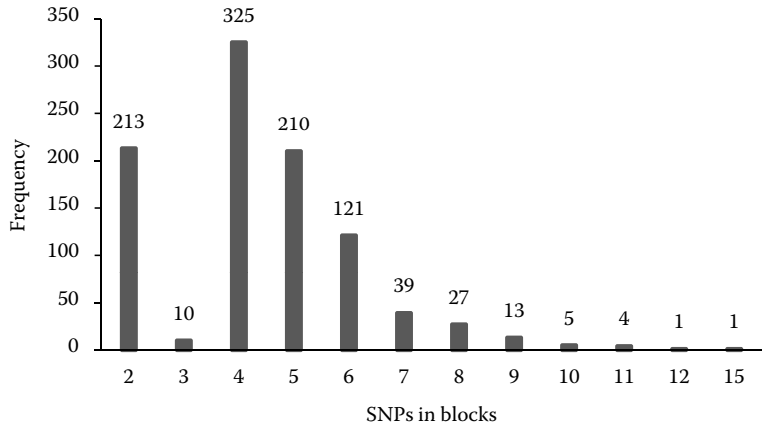

Figure 4. Frequency distribution of the number of single nucleotide polymorphisms (SNPs) forming haplotype blocks in Portuguese Holstein cattle

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good power for GWAS in the Portuguese Holstein population. Denser SNPs chips are required to achieve the recommended high LD for GWAS. Recently, high density (HD) chips have been used in GWAS (Mokry et al. 2014; O'Brien et al. 2014; Nayeri et al. 2016) and a marker interval of 5 kb can be obtained from such SNP density provided that r^2 reaches 0.59 in taurine species (O'Brien et al. 2014). Consequently, the HD chip could be more appropriate for GWAS than the 50K chip.

The haplotype blocks structures are presented in Table 3. The total number of blocks identified in the present study was 969, consisted of 4259 SNPs, and covered 159.06 Mb (6.24% of the total genome) on 29 autosomes. The maximum number of haplotypes was 91 on BTA 1, and 7 on BTA 27. The average size of haplotypes ranged from 55.73 kb on BTA 27 to 218.04 kb on BTA 5. The maximum haplotype size was 499 kb on BTA 14 and the minimum was 0.084 kb on BTA 8 (Figure 4). The maximum block coverage length on chromosome was 14 800 kb on BTA 1 and the minimum was 390.15 kb on BTA 27. The average number of SNPs forming haplotype was 4.21, with a minimum number of 2 on BTA 8 and a maximum of 15 on BTA 5 (Figure 5). The minimum number of SNPs in haplotypes was 21 on BTA 27 and the maximum was 408 on BTA 1. In the current study, the number and size of hap-

Table 3. Haplotype block structure of Portuguese Holstein cattle

BTA	Blocks (*n*)	Total block length (kb)	Block size (kb)			SNPs in blocks (*n*)	SNPs (*n*)		
			mean	min	max		mean	min	max
1	91	14 800	162.64	2	492	408	4.48	2	11
2	58	9 674.29	166.80	0.288	479	251	4.33	2	11
3	59	9 983.11	169.21	0.108	495	255	4.32	2	11
4	44	7 641	173.66	3	436	207	4.70	2	8
5	28	6 105.15	218.04	0.148	495	148	5.29	2	15
6	68	10 698	157.32	2	493	306	4.50	2	9
7	47	8 273	176.02	2	479	207	4.40	2	10
8	47	8 910.08	189.58	0.084	493	225	4.79	2	9
9	38	6 518.45	171.54	0.449	490	155	4.09	2	8
10	44	8 144	185.09	7	463	208	4.73	2	9
11	31	5 995	193.38	4	446	148	4.77	2	8
12	27	4 073.24	150.86	0.237	456	110	4.07	2	7
13	43	6 925.56	161.06	0.382	418	185	4.30	2	9
14	51	9 775.21	191.67	0.211	499	246	4.82	2	12
15	25	3 658	146.32	13	448	104	4.16	2	9
16	47	7 631	162.36	16	427	212	4.51	2	10
17	23	4 007	174.22	8	497	108	4.70	2	10
18	14	1 337	95.5	9	263	50	3.57	2	5
19	15	1 979	131.93	1	325	58	3.87	2	6
20	34	5 992	176.24	12	351	164	4.82	2	7
21	18	2 406.90	133.72	0.903	441	70	3.89	2	6
22	16	2 096	131	7	351	63	3.94	2	6
23	17	2 964	174.35	2	473	67	3.94	2	7
24	21	2 365.09	112.62	0.095	360	80	3.81	2	7
25	17	1 109	65.24	5	159	57	3.35	2	6
26	15	2 349.28	156.62	0.281	390	58	3.87	2	6
27	7	390.15	55.74	0.151	213	21	3	2	6
28	9	1 021	113.44	1	269	33	3.67	2	5
29	15	2 244	149.60	1	488	55	3.67	2	6

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Figure 5. Examples of haplotype block structure in Portuguese Holstein cattle: (**A**) haplotype block 20 on BTA 5 with maximum number of SNPs, (**B**) haplotype block 1 on BTA 8 with minimum block size, (**C**) haplotype block 30 on BTA 14 with maximum block size

lotype blocks varied according to the SNPs density on different chromosomes. On average, there was a decrease in block numbers and size with decreasing SNPs density. The same trend was found by Khatkar et al. (2007). However, the results of haplotype block analysis studies are difficult to compare due to the relationship between the marker density and the number and size of haplotype blocks. Li (2012) identified 1716 haplotype blocks in 647 Canadian Holstein bulls using 37 986 SNPs, these blocks comprised of 8249 SNPs and covered 366.78 Mb (14.41%) of the whole bovine autosomal sequence map. The average haplotype block size was 213.74 kb and the blocks were composed of 4–5 SNPs with maximum of 20 in a block and a block length of 1.172 kb on BTA7. In comparison to the current study, the total number and size of haplotype blocks obtained on Canadian Holstein bulls were higher indicating that the intensive selection and genetic drift in them were higher than in Portuguese Holstein.

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Genome Bos_Taurus_UMD_3.1 in the NCBI database was used to determine the location of genes that affect milk production traits and mastitis as reported by Ogorevc et al. (2009). Several genes inside the haplotype blocks were detected, *CSN1S2* gene was detected in haplotype block 51 on BTA 6, *IL6* and *B4GALT1* genes in haplotype blocks 6 and 33 on BTA 8, respectively, *IL1B* and *ID2* genes in haplotype blocks 19 and 29 on BTA 11 respectively, and *DGAT1* gene in haplotype block 1 on BTA 14. Marques et al. (2008) illustrated that identifying haplotype blocks can reduce the number of SNPs required for future association studies; thereby, it can decrease the costs associated with genotyping without loss of precision. Identifying haplotype blocks that contain important genes is crucial for dairy cattle selection. Some haplotype blocks, especially those containing multi genes, may extend over a large area of the genome, some having deleterious and the others beneficial effects on the animals. However, due to the high LD inside the haplotype block, a selection to increase genotype frequency of the favourite genes could be associated with the increase of the genotypic frequency of deleterious or un-favourite genes. Therefore, attention should be paid to haplotype blocks that contain important genes and they should be scanned for the presence of other deleterious genes to avoid their hazardous effects during the course of selection.

CONCLUSION

Results of the current work are consistent with those of previous studies. The extension of LD using BovineSNP50 BeadChip did not exceed 500 kb and LD parameters r^2 and D' were lower than 0.2 and 0.70, respectively, after a 70–100 kb distance. Consequently, the 50K BeadChip would have a poor power to GWAS at distances between adjacent markers greater than 70 kb. Further studies are required to investigate if a haplotype block plays a vital role in the construction of genetic correlations between traits.

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