RESEARCH ARTICLE
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Journal of Veterinary and Animal Sciences
ISSN (Print): 0971-0701, (Online): 2582-0605
https://doi.org/10.51966/jvas.2021.52.1.14-18

Linkage disequilibrium over short physical genomic distances measured using medium density SNP beadchip in native goat breeds of Kerala

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Citation: Marykutty, T., Radhika, G., Aravindakshan, T.V., Thirupathy, R., Raji, K. and Shynu, M. 2021. Linkage disequilibrium over short physical genomic distances measured using medium density SNP beadchip in native goat breeds of Kerala.*J. Vet. Anim. Sci.***52**(1): 14-18.
DOI: https://doi.org/10.51966/jvas.2021.52.1.14-18

Received: 13.06.2020 *Accepted: 20.07.2020* *Published: 01.01.2021*

Abstract

The extent of linkage disequilibrium (LD) at genome wide level is crucial in determining the effectiveness of genomics tools in livestock breeding. The present population genomic study was conducted in native goat breeds of Kerala namely; Attapady Black goats (n=24) and Malabari goats (n=24) to characterise extent of LD within 40kbp marker interval using genome wide single nucleotide polymorphism (SNP) marker data obtained by SNP50 BeadChip genotyping. Extent of LD between bi allelic markers was measured using correlation coefficient (r^2). Mean r^2 between adjacent SNP pairs across all autosomes within 40Kbp marker interval was low (Attapady Black: 0.1336; Malabari: 0.1284). The LD varied across autosomes in native goats. It was the highest for SNP pairs on Capra hircus autosome 6 (CHI 6) and the lowest for SNP pairs harboured in CHI 28 in Attapady Black goats and for SNP pairs in CHI 29 in Malabari goats. The low LD estimates indicate the genetically diverse nature of native goats. Current results also imply that denser SNP beadchip array with inter marker interval of below 40kbp would be desirable for effective genome wide association study (GWAS) and genomic selection in native goats.

***Keywords**: Linkage disequilibrium, goat, SNP BeadChip*

The goat is an important farm animal genetic resource of Kerala, constituting 45.56 per cent of its total livestock population (Government of India, 2014). Recently, the advent of draft reference goat genome, coupled with the introduction of single nucleotide polymorphism (SNP)

** Forms part of the PhD thesis of the first author submitted to Kerala Veterinary and Animal Sciences University, Pookode, Wayanad, Kerala*

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array *viz*., Illumina caprine 50K SNP BeadChip (Dong *et al.,* 2013; Tosser-Klopp *et al.,* 2014) offers unprecedented opportunities for genomic applications in goat production. The medium density caprine SNP50 BeadChip enabling cheap and fast high throughput genotyping was designed by International Goat Genome Consortium (IGGC) for global use in a wide variety of goat breeds with 53,347 SNPs distributed across genome with a median spacing of 40 Kb (Tosser-Klopp *et al.,* 2014).

Linkage disequilibrium (LD) is defined as the non-random association of alleles between two loci. The utility of medium density SNP bead chip currently available for genomic applications such as genomic selection and genome wide association study (GWAS) in a population depends on the extent of LD between SNP markers in the respective population (Kijas *et al.,* 2015). The genomic LD of native goats of Kerala was not reported earlier.

The present population genomics study was carried out in two native goat breeds of Kerala namely, Attapady Black and Malabari goats to characterise the extent of LD between SNP markers over short physical distances up to 40 Kb using genome wide SNP marker data generated by SNP50 BeadChip genotyping. The results of the present study could provide insights with respect to the usefulness of SNP50 BeadChip with median inter marker interval of 40kb for practical application in genomic predictions among native goat population of Kerala.

Materials and methods

The study population comprised of 24 each of Attapady Black and Malabari goats sampled from farmers' herds in their breeding tracts. Genomic DNA was extracted from blood samples of goats using standard phenol chloroform method (Sambrook and Russel, 2001). The DNA of 48 samples were genotyped by Illumina goat SNP50 BeadChip. Quality control of whole genome raw SNP genotype data was performed for individuals and SNPs using the Plink V.1.9 software (Purcell *et al.*, 2007). Individuals missing more than 10 per cent of genotypic data were removed. The SNPs that did not map to any autosomes of ARS1 caprine genome assembly (https://www.ncbi.nlm.nih.gov/assembly) and those that belonged to sex chromosomes were discarded. The SNPs of minor allele frequency of above 0.05, SNP call rate of ≥ 0.90 and Hardy Weinberg equilibrium exact test *P*-value above the threshold level of 0.001 were only retained for downstream analysis.

Extent of LD between bi allelic markers was measured using correlation coefficient (r^2). For a single pair of loci, *A* and *B* with a pair allele *A1* and *A2* at locus *A* and *B1* and *B2* at locus *B,* correlation coefficient (r^2) was computed as proposed by Hill and Robertson (1968)

$$r^2 = \frac{D^2}{f(A1)\, f(A2)\, f(B1)\, f(B2)}$$

Where *D = f(A1B1)f(A2B2)-f(A1B2)f(A2B1)* and *f(A1B1), f(A2B2), f(A1B2)* and*(A2B1)*are haplotype frequencies of *A1B1, A2B2, A1B2* and *A2B1* respectively; f*(A1), f(A2), f(B1), f(B2)* are allele frequencies of *A1, A2, B1 and B2* respectively.

For each breed, extent of LD (r^2) for each pair of adjacent SNPs within 40 Kb marker intervals was calculated. Analysis was done in Plink V1.9 (Purcell *et al.,* 2007).

Results and discussion

Overall LD and autosome wise LD estimate for SNPs within 40 kb interval in Attapady Black and Malabari goats are given in Table 1. Mean r^2 between adjacent SNP across all autosomes within 40Kb marker interval was 0.1336 and 0.1284 for Attapady Black and Malabari goats respectively.

The present study quantified LD of native goat breeds of Kerala utilising r^2 measure. It is a more robust LD measure when compared to the other LD measures (Ardlie *et al.*, 2002; Kijas *et al.,* 2014). At 40 Kb marker interval, the LD estimate of the native goats of Kerala was lower than that reported for important international trans-boundary goat breeds like Alpine, Boer, Nubian, Saanen and Toggenburg but comparable to that of regional goat breeds like Australian Rangeland (Brito *et al.,* 2015). Finite population size and intense

Table 1. Average linkage disequilibrium (LD, r^2) in different autosomal chromosomes for Single nucleotide polymorphisms (SNP) pairs within 40 kb interval in Attapady Black and Malabari goats of Kerala.

Chromosome	Attapady Black		Malabari	
	Number of SNP pairs	r^2	Number of SNP pairs	r^2
1	1137	0.1320	1190	0.1309
2	1022	0.1373	1045	0.1136
3	758	0.1403	799	0.1434
4	906	0.1304	957	0.1287
5	701	0.1307	738	0.1246
6	952	0.2004	1034	0.1946
7	743	0.1473	782	0.1370
8	834	0.1301	866	0.1309
9	619	0.1147	638	0.1071
10	758	0.1205	759	0.1142
11	674	0.1249	727	0.1231
12	597	0.1474	661	0.1386
13	604	0.1501	627	0.1473
14	657	0.1485	690	0.1409
15	556	0.1534	604	0.1380
16	533	0.1405	559	0.1307
17	494	0.1306	521	0.1197
18	432	0.1091	445	0.1085
19	376	0.1115	395	0.1087
20	526	0.1070	538	0.1090
21	519	0.1213	540	0.1120
22	386	0.1182	414	0.1213
23	366	0.1196	378	0.1202
24	486	0.1149	508	0.1208
25	287	0.1250	287	0.1064
26	334	0.1330	359	0.1296
27	347	0.1157	354	0.1097
28	339	0.1003	365	0.1053
29	314	0.1133	314	0.0991
All	17257	0.1336	18094	0.1284

selection undergone by improved breeds during breed formation and improvement are implicated for high genomic LD in most of the modern-day livestock breeds (Hayes, 2007). The low genomic LD in native goats indicates the diverse nature of these goat breeds.

The information about the LD among adjacent markers in the genome of native goats has practical consequences for genomic applications and predictions. The r^2 values of 0.2 and 0.3 are important indicators determining effectiveness of accuracy of genomic selection and effectiveness of association studies respectively (Meuwissen *et al.,* 2001; Ardlie *et al.,* 2002). The r^2 of 0.13 even at a short chromosomal distance of 40 kb in native goats of Kerala clearly indicates limited application of current 50K SNP panel available, for genomic selection and GWAS in native breeds of Kerala. Alternatively, more denser SNP bead array with inter marker interval of below 40 kb would be required to capture LD information needed for implementing genomic selection with reasonable accuracy in native goat breeds of Kerala.

The LD varied across autosomes in native goats (Table 1). The r^2 estimate was the highest for *Capra hircus* autosome 6 (CHI 6) (Attapady Black: 0.20; Malabari: 0.19). Nevertheless, it was the lowest for SNP pairs harboured in CHI 28 in Attapady Black goats and for SNP pairs in CHI 29 in Malabari goats.

Marked inter chromosomal heterogeneity in LD detected in the present study is in support of the observations of Mdladla *et al.* (2016) in South African goats. Selection could result in inter chromosomal heterogeneity in LD (Biegelmeyer *et al.,* 2016). Hence, higher LD estimates detected in CHI 6 of native goat breeds compared to other autosomes could be suggestive of the presence of common genomic region influencing traits that have been under selection in both breeds. Evidence of genomic regions spanning in CHI6 influencing adaptation to hot arid environment has been reported in goats (Kim *et al.,* 2015). Both native goat breeds of Kerala are well known for their adaptation to humid tropical stressors of Kerala.

Conclusion

This population genomics study characterised the extent of LD between genetic markers at short marker intervals among native goat breeds of Kerala using high throughput genomic data obtained by goat SNP50 BeadChip genotyping. The LD (r^2) between adjacent SNPs across all autosomes was low and this result was contrary to the findings in modern breeds of livestock that displayed high LD due to factors like low Ne and intense selection.

Acknowledgements

This work was partially funded by Animal Husbandry Department, Kerala. We thank ICAR-AICRP on goat improvement programme (Malabari) for the facilities and financial support provided for the collection of samples

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