Genomic inbreeding and runs of homozygosity analysis of indigenous cattle populations in southern China

Yuqiang Liu\textsuperscript{1,2*}, Guoyao Zhao\textsuperscript{1*}, Xiaojue Lin\textsuperscript{2}, Jiahao Zhang\textsuperscript{2}, Guanyu Hou\textsuperscript{3}, Luepei Zhang\textsuperscript{1}, Dewu Liu\textsuperscript{2}, Yaokun Li\textsuperscript{2}, Junya Li\textsuperscript{1*}, Lingyang Xu\textsuperscript{1*}

\textsuperscript{1} Innovation Team of Cattle Genetic Breeding, Institute of Animal Science, Chinese Academy of Agricultural Sciences, Beijing, China, \textsuperscript{2} College of Animal Science, South China Agricultural University, Guangzhou, China, \textsuperscript{3} Tropical Crop Germplasm Research Institute, Chinese Academy of Tropical Agricultural Sciences, Hainan, China

* These authors contributed equally to this work.

\textsuperscript{*} lijunya@caas.cn (JL); xulingyang@caas.cn (LX)

Abstract

Runs of homozygosity (ROH) are continuous homozygous segments from the common ancestor of parents. Evaluating ROH pattern can help to understand inbreeding level and genetic basis of important traits. In this study, three representative cattle populations including Leiqiong cattle (LQC), Lufeng cattle (LFC) and Hainan cattle (HNC) were genotyped using the Illumina BovineHD SNPs array (770K) to assess ROH pattern at genome wide level. Totally, we identified 26,537 ROH with an average of 153 ROH per individual. The sizes of ROH ranged from 0.5 to 53.26Mb, and the average length was 1.03Mb. The average of $F_{\text{ROH}}$ ranged from 0.10 (LQC) to 0.15 (HNC). Moreover, we identified 34 ROH islands (with frequency $> 0.5$) across genome. Based on these regions, we observed several breed-specific candidate genes related to adaptive traits. Several common genes related to immunity ($\text{TMEM173, MZB1}$ and $\text{SIL1}$), and heat stress ($\text{DNAJC18}$) were identified in all three populations. Three genes related to immunity ($\text{UGP2}$), development ($\text{PURA}$) and reproduction ($\text{VPS54}$) were detected in both HNC and LQC. Notably, we identified several breed-specific genes related to sperm development ($\text{BRDT}$ and $\text{SPAG6}$) and heat stress ($\text{TAF7}$) in HNC, and immunity ($\text{CDC23}$ and $\text{NME5}$) and development ($\text{WNT8}$) in LFC. Our findings provided valuable insights into understanding the genomic homozygosity pattern and promoting the conservation of genetic resources of Chinese indigenous cattle.

Introduction

Runs of homozygosity (ROH) are continuous homozygous segments inherited from common ancestors [1]. The size and count of ROH are important factors that reflect potential forces of genomic change. The generation of ROH can be influenced by inbreeding, genetic drift, population bottleneck, as well as natural and artificial selection [2]. Therefore, the detection and characterization of ROH can help to explore population structure and demographic history.
The emergence of high-throughput genotyping technology provided new methods for inbreeding assessment based on single nucleotide polymorphism (SNP). ROH were proposed as a feasible approach to measure the level of inbreeding in livestock [2–5]. The proportion of ROH in autosomal genome can be used to estimate inbreeding coefficient at individual or population levels [6]. The estimation of inbreeding coefficient based on ROH outperformed that of pedigree estimation (because pedigree is often incomplete or inaccurate) [6–8]. Moreover, ROH can be utilized to assess the distribution of homozygous fragments and identify the specific regions with high-frequency ROH on the genome [9].

Domestication and selection can reshape the genomic pattern in many livestock species [10–13]. Strict selection can be achieved by selecting a small number of superior individuals, which can reduce the haploid diversity and increase the frequency of homozygous segments containing favorable genes [14, 15]. ROH can provide valuable insight into the genetic architecture of complex traits [16]. Many studies have been carried out to detect ROH islands and identify a series of genes related to economically important traits in farm animals. For instance, Mastrangelo et al. identified genes related to milk production, immune response and resistance in four Italian cattle breeds [16]. A recent study found that many genes are related to growth, coat color and immunity in different production types of cattle breeds [17]. In local sheep, many genes related to ROH islands related to body size and reproduction were found [18–20]. Moreover, several genes related to reproductive traits, meat quality traits and energy conversion were identified within ROH islands in pig [21, 22]. Estimation of Genome-wide mapping inbreeding and the relationship between autozygosity and production traits have widely been explored in dairy and beef cattle [3, 23–26]. Moreover, analysis of ROH pattern and their relation to adaptive traits has also been carried out in many Indigenous cattle [27–31].

Indigenous cattle display genetic merits for disease resistance, parasite tolerance, heat tolerance and adapted to local environmental conditions [32]. These cattle can contribute important genetic resources for breeding programs [33]. Understanding the genetic basis underlying adaptive traits can provide valuable resources for global breeding and further help to promote the application of genetic improvement of these cattle [34]. Three indigenous cattle populations are raised in the subtropical regions of southern China (Leiqiong cattle (LQC) and Lufeng cattle (LFC) in Guangdong province, and Hainan cattle (HNC) in Hainan Province). The three breeds are draft, dual-purpure cattle. They show yellow-brown coat color, short straight horns, and small body size. After long-term domestication, these cattle have adapted to the local hot and humid environment, with the merits of strong immunity under rough feeding conditions [35–37].

Investigation of ROH pattern and identification of potentially candidate genes in indigenous cattle populations (LQC, LFC and HNC) living in hot and humid environment conditions are necessary to explain the breed-specific selection in cattle. Despite the ROH pattern of indigenous cattle from China has been explored in our previous analysis [38], ROH pattern of indigenous cattle population in southern China still remain to be explored. The aims of this work were to (i) evaluate the genome-wide ROH distribution pattern and the inbreeding level of LQC, LFC and HNC using high-density SNP arrays; (ii) identify high-frequency ROH islands across genome and investigate candidate genes in indigenous cattle.

Materials and methods

Ethics approval statement

All animals were collected in strict accordance with the Regulations of People’s Republic of China for the Administration of Laboratory Animals (2017 Revision, C12.293192, State Council, China). Animal research protocols were approved by the Institutional Animal Care
Genotyped samples

Samples were collected from three cattle populations including Leiqiong (LQC; n = 30), Lufeng (LFC; n = 33) and Hainan (HNC; n = 26), which were genotyped by Illumina BovineHD SNPs array (770K). Genomic DNA was extracted from ear tissue, and DNA with the A260/280 ratio ranging between 1.8 and 2.0 was subject to further analysis. The sample size, associated abbreviation and other information of each population are shown in Table 1. We performed quality control on SNPs array according to the following standards; (i) We removed individuals (PI-HAT value > 0.25) who are closely related as previously reported [38]. (ii) We excluded all SNPs assigned to mitochondrial chromosomes, X and Y, whereas only autosomal SNPs were used in the subsequent analysis. (iii) The individuals with genotype calling rate of more than 99% and SNPs with missing rate less than 5% were kept. (vi) SNPs were also filtered with minor allele frequency (MAF) < 0.05 and genotyping rate (geno < 0.1).

ROH estimation

Short ROH can be formed due to linkage disequilibrium across the genome. Therefore, we only detected ROH with a size greater than 0.5Mb [39, 40]. We used PLINK v1.9 to detect ROH across autosomes for each individual [41, 42]. ROH were determined as the following criteria [38]: a sliding window of 50 SNPs across the genome, the proportion of homozygous overlapping windows was 0.05, a minimum number of 100 consecutive SNPs included in a ROH, a maximum gap between consecutive homozygous SNPs of 0.1 Mb, one SNP per 50 k, and maximum two missing SNPs and one heterozygotes genotype in one ROH.

ROH classification and inbreeding coefficient

ROH were divided into three classes based on size: short (0.5-1Mb), medium (1-5Mb) and large (>5Mb) [38]. We used three methods to evaluate the inbreeding coefficient in the three populations. (i) The proportion of the genome covered by runs of homozygosity (F\textsubscript{ROH}) was estimated based on the total length of ROH divided by the length of autosomes per individual [6]. Moreover, we calculated F\textsubscript{ROH} per chromosome among the three populations [33]. (ii) compute the F\textsubscript{GRM} based on genomic relationship matrix(G) as described by previous report [42–44]. We used GCTA v1.19.2 software to calculate the F\textsubscript{GRM} according to a previous study [45]. (iii) The proportion of homozygous SNP (F\textsubscript{HOM}) based on the observed versus expected number of homozygous genotypes [9, 41, 42].

Table 1. The descriptive statistics of ROH for three Chinese indigenous cattle populations.

| Breed/Population abbreviation | Size | F\textsubscript{HOM} | F\textsubscript{ROH} | F\textsubscript{GRM} | Total ROH number\textsuperscript{a} | Average ROH number per individual | Total ROH length (Mb)\textsuperscript{b} | Average length of ROH per individual (Mb) |
|------------------------------|------|----------------------|----------------------|----------------------|-----------------------------------|-----------------------------------|----------------------------------|----------------------------------|
| LQC                          | 30   | -0.06                | 0.10                 | 0.02                 | 7760                              | 259                               | 7361                             | 245                              |
| LFC                          | 33   | 0.08                 | 0.12                 | 0.04                 | 10520                             | 319                               | 10258                            | 311                              |
| HNC                          | 26   | 0.10                 | 0.15                 | 0.04                 | 8257                              | 318                               | 9748                             | 375                              |

Note: \textsuperscript{a}. The total number of ROH events for each population.
\textsuperscript{b}. The total length of ROH events for each population. LQC: Leiqiong cattle, LFC: Lufeng cattle, HNC: Hainan cattle, F\textsubscript{HOM}: the average inbreeding coefficient based on proportion of homozygous SNP in population, F\textsubscript{ROH}: the average inbreeding coefficient based on proportion of the genome covered by runs of homozygosity in population, F\textsubscript{GRM}: the average inbreeding coefficient based on the genomic relationship matrix.

https://doi.org/10.1371/journal.pone.0271718.t001
Identification ROH island and candidate genes

We conducted a comparison analysis based on the frequency of ROH and identified candidate genes overlapping with ROH segments. In the present study, we defined ROH island based on the consensus overlapping homozygous regions with the frequency higher than 0.50 for each population [46]. In addition, the suggested frequency threshold (0.3) was considered to include more candidate genes. Moreover, candidate genes located within ROH islands were identified based on the reference genome UMD 3.1. [47].

The distribution of ROH and ROH enriched genes

To investigate the distribution of ROH across population, we estimated the common ROH segments using “—homozyg-group” option implemented in PLINK v1.9. The distributions of ROH were generated using Manhattan plot in R package CMplot (https://github.com/YinLiLin/CMplot). Moreover, the Database for Annotation, Visualization and Integrated Discovery (DAVID) was used to determine Gene Ontology (GO) terms and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways of candidate genes [48, 49].

Results

Genomic ROH distribution

After quality control, 491,515 SNPs and 89 cattle were considered for the downstream analysis. We detected a total of 26,537 ROH in 89 individuals. The size of ROH ranged from 0.5Mb to 53.3Mb in the three populations. Moreover, we observed the highest average number of ROH (319) per individual in LFC, whereas the smallest average number was observed in LQC (259). The largest total lengths of ROH with 375Mb per individual was found in HNC, whereas the smallest with 245Mb was found in LQC. The longest ROH was identified in BTA3 in HNC. Detailed summary statistics of ROH for each population were presented in Table 1.

ROH pattern and inbreeding coefficients

The total ROH length and number for each individual varied among the three populations (Fig 1). Our results showed that HNC contained a large number of long homozygous segments. In contrast, the smallest number and length for ROH was in LQC. To assess the pattern of ROH, we divided ROH into three classes according to their size, as described in previous studies [38]. The distributions of three ROH size classes were presented in Fig 2. We observed proportion of the number of ROH with large length (>5Mb) is 2% in HNC, and 0.7% in LFC and LQC. The total length of the large ROH (>5Mb) was 919Mb, and 556Mb, 2,416Mb in LFC, LQC and HNC, respectively.

We evaluated inbreeding coefficient using three methods including \( F_{\text{ROH}} \), \( F_{\text{HOM}} \) and \( F_{\text{GRM}} \). We observed the highest \( F_{\text{ROH}} \) (0.15) in HNC, whereas the minimum (0.10) in LQC. The \( F_{\text{HOM}} \) ranged from -0.06 to 0.10, whereas the \( F_{\text{GRM}} \) ranged from 0.02 to 0.04. Using these methods, our results showed similar trend for inbreeding level (Fig 3), and HNC had the highest inbreeding level. Notably, we found \( F_{\text{ROH}} \) had similar values across 29 chromosomes in HNC and LFC. However, obvious differences were found on BTA4, BTA8, BTA14 and BTA20 in LQC (Fig 4).

ROH islands distributions across genome

ROH are suited to detect signatures of selection via ROH islands, we next calculated the frequency of ROH and identified ROH islands for each chromosome. The ROH frequencies of the three populations were presented in Fig 5. We regarded ROH with a frequency larger than
Fig 1. The distributions of ROH statistics per individual for indigenous cattle populations in southern China. (A) Violin plot of the total length of ROH events per individual. (B) Violin plot the total number of ROH events per individual. LQC: Leiqiong cattle; LFC: Lufeng cattle; HNC: Hainan cattle.

https://doi.org/10.1371/journal.pone.0271718.g001

Fig 2. Total length and number of ROH for three size classes including Small (0.5 to 1 Mb), Medium (1 to 5 Mb) and Large (>5 Mb). (A) The total number of ROH for size classes. (B) The total length of ROH for three size classes. LQC: Leiqiong cattle; LFC: Lufeng cattle; HNC: Hainan cattle.

https://doi.org/10.1371/journal.pone.0271718.g002
0.5 as ROH islands and searched for candidate genes overlapping with those ROH islands. In total, we identified 7, 11, and 16 ROH islands in LQC, LFC, and HNC, respectively. Notably, we found the shared ROH islands with the highest frequency located at BTA7 in LQC, LFC, and HNC.

Gene functional annotation

Under the frequency threshold of 0.3, we identified 349 genes based on these ROH islands, and then we performed gene annotation using DAVIDv6.8, we found ten genes (OMD, ITGB8, ADAM2, PCDHGA8, PCDHG3, ITGB3, CTNNA1, PCDHB11, PCDHGA2 and PCDHGB4) that were associated to cell adhesion in HNC. Moreover, as for LFC, we found three genes (ALCAM, BSG and SEMA3B) associated to immunoglobulin domain. However, no significant GO term and KEGG pathway were found in LQC and HNC.

Breed-specific ROH genes

We identified 19, 17 and 41 genes based on the frequency threshold of 0.5 in LQC, LFC, and HNC, respectively. We found 19 common genes contained at least in two populations, and 26 breed-specific genes (Fig 6). Among them, we identified several common genes related to immunity (TMEM173, MZB1 and SIL1), and heat stress (DNAJC18) in three populations. Moreover, three common genes were related to immunity (UGP2), development (PURA) and
fecundity (VPS54) in HNC and LQC. Notably, we identified several breed-specific genes related to sperm development (BRDT and SPAG6) and heat stress (TAF7) in HNC, and immunity (CDC23 and NME5) and development (WNT87) in LFC. Detailed information about high frequency ROH and their related genes were presented in S1 Table.

Discussion

In this study, we explored the ROH pattern and assessed the inbreeding level in three indigenous Chinese cattle populations using Illumina BovineHD array. Moreover, we identified many breed-specific ROH islands across genome and mapped several candidate genes for important traits.

The distributions of total length and number of ROH implied the genetic differences among populations [50]. Consistent with a previous study [38], we found that the total number and length of ROH were large in indigenous cattle from southern China. Indigenous cattle populations showed a trend that the length and number of ROH increased from north to south [38]. In our study, we found the largest proportion of number and length of large ROH (>5Mb) were identified in HNC (Fig 1). Notably, several individuals with extreme ROH lengths (>800 Mb) were identified among the HNC. As previously reported, the large ROH (>10Mb) was generated during the recent inbreeding (up to five generation ago), whereas short ROH (<1Mb) indicates distant ancestral effect (up to 50 generation ago) [9, 33]. Also, large ROH are likely to be interrupted because of recombination. This finding was consistent with the selection history of HNC [35]. HNC is raised in Hainan province, and the limited genetic introgression occurs from other cattle populations. Thus, the unique environment condition and strict selection prompted the breed formation of HNC. In contrast, LQC had the least number of large ROH (>5Mb), which may be related to genetic introgression from
Fig 5. The distribution of ROH across autosomes in the three populations. The x-axis represents the genomic coordinate, and the y-axis displays the frequency of overlapping ROH among individuals. (A) LFC; (B) HNC; (C) LQC.

https://doi.org/10.1371/journal.pone.0271718.g005
other populations [35]. The mating or cross between outbred individuals or populations may contribute to the disruption of long ROH in the genome [40].

The detection of inbreeding level based on SNP data depends on the actual variation in inbreeding in a population, the effective population size, and the sample size [9]. Mehrnush et al. compared the inbreeding coefficient based on $F_{\text{PED}}$, $F_{\text{GRM}}$, $F_{\text{ROH}}$ and $F_{\text{TRUE}}$ (true inbreeding coefficient) in the North American Holstein dairy cattle population and they found that $F_{\text{ROH}}$ was closest to the true inbreeding coefficient [51]. We found that HNC had the highest inbreeding level by comparing the inbreeding level of three cattle populations (LFC, LQC and HNC) based on $F_{\text{PED}}$, $F_{\text{GRM}}$ and $F_{\text{HOM}}$. This was agree with previous analysis, and the effective population size of HNC is smaller than that of LQC and LFC [35]. In addition, the inbreeding level of three cattle populations (LFC, LQC and HNC) were higher than that of commercial breeds, whereas similar pattern was observed among them [39, 52–54]. Simultaneously, the high inbreeding coefficient of southern Chinese cattle populations also indicated it is urgent to design feasible mating strategies to control the level of inbreeding and maintain the effective population size for these populations. Moreover, we estimated $F_{\text{ROH}}$ for each chromosome in the three populations. HNC and LFC have similar trend on 29 chromosomes, whereas LQC was significantly different in BTA8, BTA14 and BTA20. This result can be explained that different selection pressures and recombination occurred may shape breed-specific ROH pattern on different chromosomes [55].

The formation of ROH can be influenced by inbreeding, genetic drift, population bottleneck, recombination events, as well as natural and artificial selection [12, 56]. However, ROH peaks were distributed and shared among individuals, which is likely caused by selection events, demographic history and recombination events [12, 17, 21, 55, 57]. These peaks were called hotspots or ROH islands and can be considered as the signal of selective sweeps across genome. We defined ROH regions with the frequency of more than 0.5 as ROH islands. At last, our analysis identified 34 ROH islands inclusion 45 candidate genes in the three populations. Consistent with the results from previous study [38], we found that many high-frequency ROH islands occur on BTA7 in Chinese local cattle breeds. Moreover, we found that 29 out of 45 overlapped genes.
Among them, we found three genes (TMEM173, MZB1 and SIL1) related to immunity and one gene (DNAJC18) related to heat stress in all three populations. Transmembrane protein 173 (TMEM173) activates the type I interferon-regulated innate immune response, which plays crucial role in modulating inflammation [58]. MZB1 plays an important role in the process of plasma cell differentiation [59]. Mutations of SIL1 cause Marinesco-Sjögren syndrome (MSS), which is a neurodegenerative disorder [60]. In a previous study, a member of the heat shock protein family (DNAJC18) responding to heat stress has been identified in East African Shorthorn Zebu cattle [61]. These results indicated that the identification of candidate genes for the indigenous cattle populations in southern China may help to explain the genetic basis of adaptation for the humid and hot environments. We also found three genes including UGP2, PURA and VPS54 related to immunity, reproduction and development in HNC and LQC. UGP2 plays an essential role in promoting HCC cell migration and tumor metastasis. Mutations in PURA may alter normal brain development and impair neuronal function, leading to developmental delay [62]. VPS54 null mutation may cause embryonic lethality [63].

Notably, we found three breed-specific genes (WNT8A, NME5 and CDC23) related to body weight and immunity in LFC. The WNT8A contains four single-nucleotides polymorphisms that have an obviously relationship with the height and length of Qinchuan cattle [64]. WNT8A was related to the dwarf size in Chinese southern cattle. NME5 was identified as a candidate gene for primary ciliary dyskinesia and hydrocephalus cases [65]. CDC23 is a critical regulator of cell cycle and cell growth, and may involve with thyroid cancer initiation and progression [66]. Remarkably, we found three genes (TAF7, SPAG6 and BRDT) related to immunity and reproduction in HNC. TAF7 can regulate the expression of heat shock protein genes and enhance efficient recovery of cells challenged to thermal stress [67]. SPAG6 acts a crucial role in immuno-regulation, and participate in the occurrence and progression of human cancers. SPAG6 was also reported that can regulate tumor cell proliferation, apoptosis, invasion, and metastasis [68]. BRDT is essential for the normal progression of spermatogenesis, and mutations in BRDT can cause male sterility [69]. We suspected that the immune-related genes have been identified among populations, which may reflect the effects of long-term selection for LFC and HNC in the harsh environments.

Conclusions

In summary, we assessed the ROH pattern, inbreeding level and identified several candidate genes related to important traits in three indigenous cattle populations in southern China. Our findings provided important insights into understanding the genetic basis of adaptive traits and facilitate the protection and breeding management of indigenous cattle population.

Supporting information

S1 Table. The descriptive statistics about the high frequency ROH and candidate genes for indigenous cattle populations in southern China. (XLSX)

Acknowledgments

The authors would like to thank Xiaojue Lin and Jiahao Zhang for sample collection.

Author Contributions

Conceptualization: Lingyang Xu.
Formal analysis: Guoyao Zhao, Lingyang Xu.  
Methodology: Yuqiang Liu.  
Resources: Xiaojue Lin, Jiahao Zhang, Guanyu Hou, Luepei Zhang, Dewu Liu, Yaokun Li.  
Software: Yuqiang Liu.  
Writing – original draft: Yuqiang Liu, Guoyao Zhao.  
Writing – review & editing: Junya Li, Lingyang Xu.  

References
1. Gibson J, Morton NE, Collins A. Extended tracts of homozygosity in outbred human populations. Hum Mol Genet. 2006; 15(5):789–95. Epub 2006/01/27. https://doi.org/10.1093/hmg/ddi493 PMID: 16436455.
2. Curik I, Ferencakovic M, Soltkner J. Inbreeding and runs of homozygosity: A possible solution to an old problem. Livestock Science. 2014; 166:26–34. https://doi.org/10.1016/j.livsci.2014.05.034
3. Ferencakovic M, Soltkner J, Kaps M, Curik I. Genome-wide mapping and estimation of inbreeding depression of semen quality traits in a cattle population. J Dairy Sci. 2017; 100(6):4721–30. Epub 2017/04/25. https://doi.org/10.3168/ds.2016-12164 PMID: 28434751.
4. Nandolo W, Utsunomiya YT, Meszaros G, Wurzinger M, Khayadzadeh N, Torrecilha RBP, et al. Mis-identification of runs of homozygosity islands in cattle caused by interference with copy number variation or large intermarker distances. Genet Sel Evol. 2018; 50(1):43. Epub 2018/08/24. https://doi.org/10.1186/s12711-018-0414-x PMID: 29667329; PubMed Central PMCID: PMC566898.
5. Zavarez LB, Utsunomiya YT, Carmo AS, Neves HH, Carvalheiro R, Ferencakovic M, et al. Assessment of autozygosity in Nellore cows (Bos indicus) through high-density SNP genotypes. Genet Sel Evol. 2018; 50(1):43. Epub 2018/08/24. https://doi.org/10.1186/s12711-018-0414-x
6. McQuillan R, Leutenegger AL, Abdel-Rahman R, Franklin CS, Pericic M, Barac-Lauc L, et al. Runs of homozygosity in European populations. Am J Hum Genet. 2006; 83(3):359–72. Epub 2006/09/02. https://doi.org/10.1086/499438 PMID: 16760389; PubMed Central PMCID: PMC2556426.
7. Howrigan DP, Simonson MA, Keller MC. Detecting autozygosity through runs of homozygosity: A comparison of three autozygosity detection algorithms. BMC Genomics. 2011; 12(460). https://doi.org/10.1186/1471-2164-12-460 PMID: 21943305
8. Carothers AD, Rudan I, Kolcic I, Polasek O, Hayward C, Wright AF, et al. Estimating Human Inbreeding Coefficients: Comparison of Genealogical and Marker Heterozygosity Approaches. Annals of Human Genetics. 2006; 70(5):66–76. https://doi.org/10.1111/j.1469-1809.2006.00263.x PMID: 16907711
9. Keller MC, Visscher PM, Goddard ME. Quantification of Inbreeding Due to Distant Ancestors and Its Detection Using Dense Single Nucleotide Polymorphism Data. Genetics. 2011; 189(1):237–49. https://doi.org/10.1534/genetics.111.130922 PMID: 21705750
10. Edea Z, Dadi H, Dessie T, Kim KS. Genomic signatures of high-altitude adaptation in Ethiopian sheep populations. Genes Genomic. 2019; 41(8):973–81. Epub 2019/05/04. https://doi.org/10.1007/s13258-019-00829-y PMID: 31119684.
11. Moon S, Kim TH, Lee KT, Kwak W, Lee T, Lee SW, et al. A genome-wide scan for signatures of directional selection in domesticated pigs. BMC Genomics. 2015; 16:130. Epub 2015/03/15. https://doi.org/10.1186/s12864-015-1330-x PMID: 25765548; PubMed Central PMCID: PMC4349229.
12. Peripolli E, Munari DP, Silva M, Lima ALF, Irgang R, Baldi F. Runs of homozygosity: current knowledge and applications in livestock. Anim Genet. 2017; 48(3):255–71. Epub 2016/12/03. https://doi.org/10.1111/age.12526 PMID: 27910110.
13. Taye M, Yoon J, Dessie T, Cho S, Oh SJ, Lee HK, et al. Deciphering signature of selection affecting beef quality traits in Angus cattle. Genes Genomic. 2018; 40(1):63–75. Epub 2018/06/13. https://doi.org/10.1007/s13258-017-0610-2 PMID: 29892901.
14. Upadhyay M, Bortoluzzi C, Barbato M, Ajmone-Marsan P, Colli L, Ginja C, et al. Deciphering the patterns of genetic admixture and diversity in southern European cattle using genome-wide SNPs. Evol Appl. 2019; 12(5):951–63. Epub 2019/05/14. https://doi.org/10.1111/eva.12770 PMID: 31080507; PubMed Central PMCID: PMC6503822.
15. Zhang Q, Gulbrandtsen B, Bosse M, Lund MS, Sahana G. Runs of homozygosity and distribution of functional variants in the cattle genome. BMC Genomics. 2015; 16(1). https://doi.org/10.1186/s12864-015-1715-x PMID: 26198692
Genomic inbreeding and runs of homozygosity analysis on indigenous cattle populations

16. Mastrangelo S, Sardina MT, Tolone M, Di Gerlando R, Sutera AM, Fontanesi L, et al. Genome-wide identification of runs of homozygosity islands and associated genes in local dairy cattle breeds. Animal. 2018; 12(12):2480–8. Epub 2018/03/27. https://doi.org/10.1017/S1751731118000629 PMID: 29576040.

17. Szmatał T, Gurgul A, Jasielczuk I, Ząbek T, Ropka-Molik K, Litwinczuk Z, et al. A Comprehensive Analysis of Runs of Homozygosity of Eleven Cattle Breeds Representing Different Production Types. Animals. 2019; 9(12). https://doi.org/10.3390/ani9121024 PMID: 31775271.

18. Mastrangelo S, Ciani E, Sardina MT, Sottile G, Pilia F, Portolano B, et al. Runs of homozygosity reveal genome-wide autozygosity in Italian sheep breeds. Anim Genet. 2018; 49(1):71–81. Epub 2018/01/16. https://doi.org/10.1111/age.12634 PMID: 29333609.

19. Purfield DC, McParland S, Wall E, Berry DP. The distribution of runs of homozygosity and selection signatures in six commercial meat sheep breeds. PLoS One. 2017; 12(5):e0176780. Epub 2017/05/04. https://doi.org/10.1371/journal.pone.0176780 PMID: 28463982; PubMed Central PMCID: PMC5413029.

20. Signer-Hasler H, Burren A, Ammann P, Drogemuller C, Flury C. Runs of homozygosity and signatures of selection: a comparison among eight local Swiss sheep breeds. Anim Genet. 2019; 50(5):512–25. Epub 2019/08/01. https://doi.org/10.1111/age.12828 PMID: 31365135.

21. Szmatał T, Jasielczuk I, Semik-Gurgul E, Szyndler-Nedza M, Blicharski T, Szulc K, et al. Detection of runs of homozygosity in conserved and commercial pig breeds in Poland. J Anim Breed Genet. 2020. Epub 2020/05/04. https://doi.org/10.1111/jbg.12462 PMID: 32352048.

22. Xie R, Shi L, Liu J, Deng T, Wang L, Liu Y, et al. Genome-Wide Scan for Runs of Homozygosity Identification Candidate Genes in Three Pig Breeds. Animals (Basel). 2019; 9(8). Epub 2019/08/04. https://doi.org/10.3390/ani9080518 PMID: 31374971; PubMed Central PMCID: PMC6720638.

23. Martikainen K, Sironen A, Uimari P. Estimation of intrachromosomal inbreeding depression on female fertility using runs of homozygosity in Finnish Ayrshire cattle. J Dairy Sci. 2018; 101(12):11097–107. Epub 2018/10/15. https://doi.org/10.3168/jds.2018-14805 PMID: 30316595.

24. Cesaran A, Gaspa G, Pauciullo A, Degano L, Vicario D, Macciotta N. Genome-wide analysis of homozygous regions in six commercial pig breeds in Poland. J Anim Breed Genet. 2020. Epub 2020/12/03. https://doi.org/10.1111/jbg.12502 PMID: 33263211.

25. Kim K, Jung J, Caetano-Anolles K, Sung S, Yoo D, Choi BH, et al. Artificial selection increased body weight but induced increase of runs of homozygosity in Hanwoo cattle. PLoS One. 2018; 13(3):e0193701. Epub 2018/03/22. https://doi.org/10.1371/journal.pone.0193701 PMID: 29561881; PubMed Central PMCID: PMC5862439.

26. Zhao G, Liu Y, Niu Q, Zheng X, Zhang T, Wang Z, et al. Runs of homozygosity analysis reveals consens-us homozygous regions affecting production traits in Chinese Simmental beef cattle. BMC Genomics. 2021; 22(1). https://doi.org/10.1186/s12866-021-07992-6 PMID: 34548021.

27. Zsolnai A, Marotí-Agots A, Kovacs A, Balteanu AV, Kaltenexer E, Anton I. Genetic position of Hungarian Grey among European cattle and identification of breed-specific markers. Animal. 2020; 14(9):1786–92. Epub 2020/04/07. https://doi.org/10.1017/S1751731120006343 PMID: 32248869.

28. Saravanan KA, Panigrahi M, Kumar H, Parida S, Bhushan B, Gaur GK, et al. Genomic scans for selection signatures revealed candidate genes for adaptation and production traits in a variety of cattle breeds. Genomics. 2021; 113(3):955–63. Epub 2021/02/22. https://doi.org/10.1016/j.ygeno.2021.02.006 PMID: 33810795.

29. Cesaran A, Sorbolini S, Cricione A, Bordonaro S, Pulina G, Battacone G, et al. Genome-wide variability and selection signatures in Italian island cattle breeds. Anim Genet. 2018; 49(5):371–83. Epub 2018/05/09. https://doi.org/10.1111/age.12828 PMID: 30070013.

30. Xu L, Zhang WG, Shen HX, Zhang Y, Zhao YM, Jia YT, et al. Genome-wide scanning reveals genetic diversity and signatures of selection in Chinese indigenous cattle breeds. Livestock Science. 2018; 216:100–8. https://doi.org/10.1016/j.livsci.2018.08.005.

31. Ben Jemaa S, Rahal O, Gaouar SBS, Mastrangelo S, Boussaha M, Ciani E. Genomic characterization of Algerian Guelmoise cattle and their genetic relationship with other North African populations inferred from SNP genotyping arrays. Livestock Science. 2018; 217:19–25. https://doi.org/10.1016/j.livsci.2018.09.009.

32. Karimi K, Strucken EM, Moghaddar N, Ferdosi MH, Esmaillizadeh A, Gondro C. Local and global patterns of admixture and population structure in Iranian native cattle. BMC Genet. 2016; 17(1):108. Epub 2016/07/16. https://doi.org/10.1186/s12863-016-0416-z PMID: 27418004; PubMed Central PMCID: PMC4946207.

33. Mastrangelo S, Tolone M, Di Gerlando R, Fontanesi L, Sardina MT, Portolano B. Genomic inbreeding estimation in small populations: evaluation of runs of homozygosity in three local dairy cattle breeds. Animal. 2016; 10(5):746–54. Epub 2016/04/15. https://doi.org/10.1017/S1751731115002943 PMID: 27076405.
34. Strandén I, Kantanen J, Russo I-RM, Orozco-terWengel P, Bruford MW. Genomic selection strategies for breeding adaptation and production in dairy cattle under climate change. Heredity. 2019; 123 (3):307–17. https://doi.org/10.1038/s41437-019-0207-1 PMID: 30886391

35. Liu Y, Xu L, Yang L, Zhao G, Li J, Liu D, et al. Discovery of Genomic Characteristics and Selection Signatures in Southern Chinese Local Cattle. Frontiers in Genetics. 2020;11. https://doi.org/10.3389/fgene.2020.033052 PMID: 33391332

36. Gao Y, Gautier M, Ding X, Zhang H, Wang Y, Wang X, et al. Species composition and environmental adaptation of indigenous Chinese cattle. Sci Rep. 2017; 7(1):16196. Epub 2017/11/25. https://doi.org/10.1038/s41598-017-16438-7 PMID: 29170422; PubMed Central PMCID: PMC5700937.

37. Wang K, Cao Y, Rong Y, Ning Q, Jia P, Huang Y, et al. A Novel SNP in EIF2AK4 Gene Is Associated with Thermal Tolerance Traits in Cattle. Animals (Basel). 2019; 9(6). Epub 2019/06/30. https://doi.org/10.3390/ani9060375 PMID: 31248194; PubMed Central PMCID: PMC6617145.

38. Xu L, Zhao G, Yang L, Zhu B, Chen Y, Zhang L, et al. Genomic Patterns of Homozygosity in Chinese Local Cattle. Sci Rep. 2019; 9(1):16977. Epub 2019/11/20. https://doi.org/10.1038/s41598-019-53274-3 PMID: 31740716; PubMed Central PMCID: PMC6861314.

39. Dixit SP, Singh S, Ganguly I, Bhatia AK, Sharma A, Kumar NA, et al. Genome-Wide Runs of Homozygosity Revealed Selection Signatures in Bos indicus. Frontiers in Genetics. 2020;11. https://doi.org/10.3389/fgene.2020.00092 PMID: 32153647

40. Purfield DC, Berry DP, McParland S, Bradley DG. Runs of homozygosity and population history in cattle. BMC Genetics. 2012; 13(70). https://doi.org/10.1186/1471-2156-13-70 PMID: 22888585

41. Chang CC, Chow CC, Tellier LCAM, Vattikuti S, Purcell SM, Lee JJ. Second-generation PLINK: rising to the challenge of larger and richer datasets. GigaScience. 2015; 4(1). https://doi.org/10.1186/s13742-015-0047-8 PMID: 25722852

42. Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MA, Bender D, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. Am J Hum Genet. 2007; 81(3):559–75. Epub 2007/08/19. https://doi.org/10.1086/519795 PMID: 17701901; PubMed Central PMCID: PMC1950838.

43. Bjelland DW, Weigel KA, Vukasinovic N, Nkrumah JD. Evaluation of inbreeding depression in Holstein cattle using whole-genome SNP markers and alternative measures of genomic inbreeding. Journal of Dairy Science. 2013; 96(7):4697–706. https://doi.org/10.3168/jds.2012-6435 PMID: 23684028

44. VanRaden PM, Olson KM, Wiggans GR, Cole JB, Tooker ME. Genomic inbreeding and relationships among Holsteins, Jerseys, and Brown Swiss. Journal of Dairy Science. 2011; 94(11):5673–82. https://doi.org/10.3168/jds.2012-4453-z PMID: 30223795

45. Dixit SP, Singh S, Ganguly I, Bhatia AK, Sharma A, Kumar NA, et al. Genome-Wide Runs of Homozygosity Revealed Selection Signatures in Bos indicus. Frontiers in Genetics. 2020;11. https://doi.org/10.3389/fgene.2020.00092 PMID: 32153647

46. Purfield DC, Berry DP, McParland S, Bradley DG. Runs of homozygosity and population history in cattle. BMC Genetics. 2012; 13(70). https://doi.org/10.1186/1471-2156-13-70 PMID: 22888585

47. Chang CC, Chow CC, Tellier LCAM, Vattikuti S, Purcell SM, Lee JJ. Second-generation PLINK: rising to the challenge of larger and richer datasets. GigaScience. 2015; 4(1). https://doi.org/10.1186/s13742-015-0047-8 PMID: 25722852

48. Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MA, Bender D, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. Am J Hum Genet. 2007; 81(3):559–75. Epub 2007/08/19. https://doi.org/10.1086/519795 PMID: 17701901; PubMed Central PMCID: PMC1950838.

49. Bjelland DW, Weigel KA, Vukasinovic N, Nkrumah JD. Evaluation of inbreeding depression in Holstein cattle using whole-genome SNP markers and alternative measures of genomic inbreeding. Journal of Dairy Science. 2013; 96(7):4697–706. https://doi.org/10.3168/jds.2012-6435 PMID: 23684028

50. VanRaden PM, Olson KM, Wiggans GR, Cole JB, Tooker ME. Genomic inbreeding and relationships among Holsteins, Jerseys, and Brown Swiss. Journal of Dairy Science. 2011; 94(11):5673–82. https://doi.org/10.3168/jds.2012-4453-z PMID: 30223795

51. Strandén I, Kantanen J, Russo I-RM, Orozco-terWengel P, Bruford MW. Genomic selection strategies for breeding adaptation and production in dairy cattle under climate change. Heredity. 2019; 123 (3):307–17. https://doi.org/10.1038/s41437-019-0207-1 PMID: 30886391

52. Liu Y, Xu L, Yang L, Zhao G, Li J, Liu D, et al. Discovery of Genomic Characteristics and Selection Signatures in Southern Chinese Local Cattle. Frontiers in Genetics. 2020;11. https://doi.org/10.3389/fgene.2020.033052 PMID: 33391332

53. Dunker SC, Brem G, Neuditschko M. Analysis of ROH patterns in

54. VanRade n PM, Olson KM, Wiggans GR, Cole JB, Tooker ME. Genom ic inbreeding and relationships among Holsteins, Jerseys, and Brown Swiss. Journal of Dairy Science. 2011; 94(11):5673–82. https://doi.org/10.3168/jds.2012-4453-z PMID: 30223795
polymorphism analysis. Plos One. 2020; 15(11). https://doi.org/10.1371/journal.pone.0242200 PMID: 33196682

54. Chiang T-Y, Addo S, Klingel S, Hinrichs D, Thaller G. Runs of Homozygosity and NetView analyses provide new insight into the genome-wide diversity and admixture of three German cattle breeds. Plos One. 2019; 14(12). https://doi.org/10.1371/journal.pone.0225847 PMID: 31800604

55. Bosse M, Megens HJ, Madsen O, Paudel Y, Frantz LA, Schook LB, et al. Regions of homozygosity in the porcine genome: consequence of demography and the recombination landscape. PLoS Genet. 2012; 8(11):e1003100. Epub 2012/12/05. https://doi.org/10.1371/journal.pgen.1003100 PMID: 23209444; PubMed Central PMCID: PMC3510040.

56. Ceballos FC, Joshi PK, Clark DW, Ramsay M, Wilson JF. Runs of homozygosity and NetView analyses provide new insight into the genome-wide diversity and admixture of three German cattle breeds. Plos One. 2019; 14(12). https://doi.org/10.1371/journal.pone.0225847 PMID: 31800604

57. Kim E-S, Cole JB, Huson H, Wiggans GR, Van Tassell CP, Crooker BA, et al. Effect of Artificial Selection on Runs of Homozygosity in U.S. Holstein Cattle. PLoS ONE. 2013; 8(11). https://doi.org/10.1371/journal.pone.0080813 PMID: 24348915

58. Moua P, Checketts M, Xu LG, Shu HB, Reyland ME, Cusick JK. RELT family members activate p38 and induce apoptosis by a mechanism distinct from TNFR1. Biochem Biophys Res Commun. 2017; 491(1):25–32. Epub 2017/07/10. https://doi.org/10.1016/j.bbrc.2017.07.022 PMID: 28688764; PubMed Central PMCID: PMC5617334.

59. Kanda M, Tanaka C, Kobayashi D, Tanaka H, Shimizu D, Shibata M, et al. Epigenetic suppression of the immunoregulator MZB1 is associated with the malignant phenotype of gastric cancer. Int J Cancer. 2016; 139(10):2290–8. Epub 2016/07/08. https://doi.org/10.1002/ijc.30286 PMID: 27459504.

60. Roos A, Kollipara L, Buchkremer S, Labisch1 T, Brauers E, Gatz C, et al. Cellular Signature of SIL1 Depletion: Disease Pathogenesis due to Alterations in Protein Composition Beyond the ER Machinery. Mol Neurobiol. 2016; 53. https://doi.org/10.1007/s12035-015-9456-z PMID: 26461856

61. Bahbahani H, Clifford H, Wragg D, Mbole-Kariuki MN, Van Tassell C, Sonstegaard T, et al. Signatures of positive selection in East African Shorthorn Zebu: A genome-wide single nucleotide polymorphism analysis. Sci Rep. 2015; 5:11729. Epub 2015/07/02. https://doi.org/10.1038/srep11729 PMID: 26130263; PubMed Central PMCID: PMC4486961.

62. Tanaka AJ, Bai R, Cho MT, Anyane-Yeboa K, Ahimaz P, Wilson AL, et al. De novo mutations in PURA are associated with hypotonia and developmental delay. Cold Spring Harb Mol Case Stud. 2015; 1(1): a000356. Epub 2016/05/06. https://doi.org/10.1101/mcs.a000356 PMID: 27148565; PubMed Central PMCID: PMC4850980.

63. Karlsson P, Droce A, Moser JM, Cuhilmann S, Padilla CO, Heimann P, et al. Loss of vps54 function leads to vesicle traffic impairment, protein mis-sorting and embryonic lethality. Int J Mol Sci. 2013; 14 (6):10908–25. Epub 2013/05/28. https://doi.org/10.3390/ijms140610908 PMID: 23708095; PubMed Central PMCID: PMC3709709.

64. Huang Y-Z, Zou Y, Lin Q, He H, Zheng L, Zhang Z-J, et al. Effects of genetic variants of the bovine WNT8A gene on nine important growth traits in beef cattle. Journal of Genetics. 2017; 96(4):535–44. https://doi.org/10.1007/s12041-017-0804-9 PMID: 28947701

65. Anderegg L, Gut MIH, Hetzel U, Howarth EW, Leuthard F, stila KK, et al. MME5 frameshift variant in Alaskan Malamutes with primary ciliary dyskinesia. PLOS Genetics. 2019; 15(9):e1008378. https://doi.org/10.1371/journal.pgen.1008378 PMID: 31479451

66. Zheng DF, Wang Q, Wang JP, Bao ZQ, Wu SW, Ma L, et al. The Emerging Role of Sperm-Associated Antigen 6 Gene in the Microtubule Function of Cells and Cancer. Mol Ther Oncolytics. 2019; 15:101–7. Epub 2019/10/30. https://doi.org/10.1016/j.omto.2019.08.011 PMID: 31660426; PubMed Central PMCID: PMC6807308.

67. Mantorola M, Brown TM, Oh MY, Caryn C, Gonzalez BJ, Wolgemuth DJ. BRDT is an essential epigenetic regulator for proper chromatin organization, silencing of sex chromosomes and crossover formation in male meiosis. PLoS Genet. 2018; 14(3):e1007209. Epub 2018/03/08. https://doi.org/10.1371/journal.pgen.1007209 PMID: 29513658; PubMed Central PMCID: PMC5841650.