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Review

Linkage disequilibrium, genomic inbreeding and effective populations size to unravel population history

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The use of single nucleotide polymorphism (SNP) data had become commonplace in animal breeding activities and management of livestock populations. The cost-effective genotyping allowed us to assess entire populations and learn about their history on the genomic level. This paper reviews several approaches that are commonly used in the context of genomic diversity in livestock, such as the linkage disequilibrium (LD) and assessment of autozygosity via runs of homozygosity (ROH). Both methods, however, are being used to assess the impact of natural or artificial selection on the livestock genome. Apart from these selection signatures, both the LD and ROH are used to assess the effective population size (Ne), which likewise, serves as a diversity management tool and describes the historical events in populations.

Keywords: livestock, genomics, SNP, selection signatures, diversity

1 Introduction

The availability of molecular markers, most importantly, single nucleotide polymorphisms (SNP) enables their use for a more detailed evaluation of genetic diversity. The utilization of such precise tools is becoming a necessity to monitor the animal genetic resources, to develop populations further (Moravčíková & Kasarda, 2020). One of the most important characteristics of genetic diversity is the effective population size (N_e) that is often used as a metric to determine the endangerment status of a breed. The N_e is characterised as the size of the ideal population that shows the same extent of genetic drift or inbreeding levels as the real population in question (Wright, 1931). There is a range of methods available to determine effective population size, including non-genomic pedigree and high-density genotype data. From the genomic methods, the estimations based on linkage disequilibrium (LD) and inbreeding assessed via runs of homozygosity (ROH) are the most often used. In this work, we will describe the role of LD, genomic inbreeding via ROH and N_e, and highlight their common characteristics to assess population history for the needs of animal breeding and conservation practices.

1.1 Linkage disequilibrium

Alleles near each other in the genome are inherited together in a non-independent fashion (i.e. contrary to Mendel's law of independent assortment) as blocks or haplotype sequences of parents (Ardlie et al., 2002). As an outcome of this process, non-random connections and correlations build up between the alleles, also called linkage disequilibrium (LD). The correlation could be caused by the proximity of alleles, but it is often driven by evolutionary processes, such as natural and artificial selection, controlled mating, recombination and genetic drift (Reich et al., 2001; Khatkar et al., 2008). Indeed, the LD dependent genome architecture, especially regions with low recombination rate and extensive low LD levels are enriched for deleterious variants, thus indicating negative selection (Gazal, 2017). On the other hand, high LD levels are commonly regarded as positive selection signatures (Fariello et al., 2017).

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There are several parameters available to estimate the extent of LD, such as parameters D and D' for which the range is constrained between -1 and 1 (Sved & Hill, 2018). The most frequently used parameter is the r^2, the squared correlation coefficient between alleles (Hill & Robertson, 1968). This LD estimation method is considered the most effective way for biallelic markers, while it also enables to compute LD in small samples (Khatkar et al., 2008). The r^2 ranges between 0 and 1. The $r^2 = 0$ means that the genotypes on two loci are totally independent from each other, while $r^2 = 1$ means that knowing a genotype on one locus provides exact information about the other. The r^2 values between 0 and 1 indicate the strength of the relationship between the two extremes. The strength of LD are influenced by various factors, such as selection, migration, genetic drift, mutation, population size or recombination rate (Karimi et al., 2015). The extent of LD in various taurine and indicine cattle populations was evaluated by Pérez O'Brien et al. (2014).

The LD as a genomic phenomenon is the basis for a wide range of analyses in livestock, such as genomic selection, imputation, mapping of the genome, genome-wide association studies (GWAS) or selection signatures. In the estimation of genomic diversity, parameters LD is one option to assess effective population size.

The primary goal of genomic selection is to assess the genomic breeding value of an individual, preferably at a young age. Its basis was outlined in Meuwissen et al. (2001) and relied on the identification of potentially all quantitative trait loci (QTLs) for the trait on the genome. The identification of the QTLs is done by utilisation dense molecular markers (e.g. SNPs) distributed throughout the genome. With a dense-enough SNP coverage, each of the unobserved causal QTL is in an LD with one or more known SNP variants, enabling their use to estimate genomic breeding values. Genomic selection became the current practice in animal breeding (Hickey et al., 2017) with a potential to double genetic gain (Georges et al., 2019).

The LD also plays a crucial role in the genome mapping and the trait-specific GWAS. The studies have gradually increased in sample sizes, rates of discovery, the number of traits studied (Mills & Rahal, 2019), and the number of models used to identify the causal variants (Schmid & Bennewitz, 2017). The casual variants are usually not genotyped themselves, but are in an LD with one or more genotyped SNPs (Tam et al., 2019). Based on the LD map of dairy cattle breeds, it was suggested that an LD above $r^2 = 0.3$ could give sufficient power in GWAS analyses. Given the decrease of LD with the base-pair distance on the genome (LD decay), the LD above 0.3 is maintained up to 0.5 Mb in dairy cattle. This also means that there is a need for ca. 50 thousand markers evenly distributed in the genome to conduct whole-genome association studies (McKay et al., 2007). In beef cattle, the LD is maintained over shorter distances, with useful LD (i.e. providing sufficient power in GWAS and similar analyses) only up to 0.2 Mb (Lu et al., 2012; Porto-Neto et al., 2014). In sheep, Mastrangelo et al. (2014) found LD only 0.15 ±0.20 between neighbouring markers, confirming the study of Kijas et al. (2014) about lower LD in sheep, compared to other livestock species. This also means that more markers would be needed to detect signals from genome-wide association studies and similar analyses. On the other hand, in pigs the LD seems to be stronger, with useful LD $r^2 > 0.2$ spanning to 1.0–1.5 Mb (Uimari & Tapio, 2011). While the reason behind differences in LD between species is not entirely clear, we assume that it is connected to different evolutionary and selection pressures in different livestock populations.

The LD is also one of the central indicators to map and evaluate the effects of selection on the livestock genome (Qanbari, 2020). The long and unbroken haplotypes with high LD among loci indicate the section of the genome responding to an adaptive quality (Sabeti et al., 2002). The increased LD as the direct consequence of selection was also confirmed in Kim et al. (2013), where an unselected control population was compared to contemporary elite sires. Differences due to the 50 years of selection acting in the livestock genome were detected, manifesting in different LD structure and significant changes in the autozygosity levels, thus the inbreeding coefficients in the population. The increased LD within parts of the genome indicates a reduced recombination rate, likely because of an occurrence of a beneficial mutation. The LD-based selection signature detection methods are especially useful to detect variants under partial or soft selective sweep (Saravanan et al., 2020). The two most important LD based methods used in this context are the EHH (Sabeti et al., 2002) and its derived method of iHS (Voight et al., 2006). The iHS method was also utilised in an approach that combines outcomes of different selection signature methods in dairy and beef cattle breeds (Utsunomiya et al., 2013, Kasarda et al., 2015). The detection of differences in LD variability was used to detect selection signatures between beef cattle breeds in Moravčíková et al. (2019). The advantage of the LD based methods is the possibility to identify the age of each segment, thus the age of the selection signature, based on the length of the LD segment (Otto, 2000).

1.2 Genomic inbreeding coefficient

One of the most important parameters for assessing genetic diversity on the genomic level is the homozygosity, ideally in the form of runs of homozygosity

(ROH). These ROH segments in an individual come from joined identical haplotypes from common ancestors of parents. These could be found in the genomes of all livestock and human populations.

The ROH are widely used in the management and characterisation of animal genetic resources. They can be used for explanation and description of evolutionary history, demographic information, for assessment of relatedness and identification of selection signatures (Rebelato & Caetano, 2018). The frequency, size and distribution of ROH segments in the genome are influenced by multiple factors, such as natural and artificial selection, recombination, linkage disequilibrium, the structure of the population, as well as the extent of inbreeding (Peripolli et al., 2016). The formation of ROH segments as a result of recombination activities in the genome shows the long term impact of demographic processes on the population. Thus, the study of ROH segments is also suited for comparative genomics of species (Brüniche-Olsen et al., 2018). The ROH segments are frequently used to assess the presence of natural or artificial selection on the genome (e.g. Signer-Hasler et al., 2019) and identify candidate genes of interest (e.g. Mastrangelo et al., 2014).

The most frequent use of ROH is for estimation of inbreeding coefficient, as the proportion of ROH segments from the total length of the autosome covered by SNPs (McQuillan et al., 2008). This measure of inbreeding is considered to be more precise than the one based on a conventional pedigree (Zhang et al., 2015). The length of the ROH segments also denotes the time when the common ancestor was active in the population. Longer ROH segments indicate that the common ancestor was more recent, while ROH segments of 1Mb point to the common ancestor about 50 generations away in the past. Segments of 16Mb point to common ancestors only three generations away (Ferenčaković et al., 2013). Mastrangelo et al. (2014) further include the minimal limitation of ROH to 1 Mb to avoid homozygous segments caused only by LD. As shown in Kim et al. (2013), in humans, the ROH are significantly shorter compared to cattle, which is likely caused by difference in selection intensity. Generally, the ROH segments are shorter and less frequent in large populations compared to isolated and small populations. Crossbred populations have the smallest ROH amount, while populations undergoing close inbreeding show very long continuously homozygous segments (Ceballos et al., 2018).

Some of the disorders manifest when two recessive alleles come into homozygous state. These alleles could also come from a common ancestor, thus appear in the identified ROH. This means that ROH could be used for mapping of unwanted mutations that cause the so-called inbreeding depression. Such mutations lead to genetic disorders, decrease in production, reproduction, functional and other traits (Curik et al., 2017; Baes et al., 2019). ROH segments are randomly distributed in the genome, with different frequency of occurrence. In certain parts of the genome, they could not be found, in other parts abundant to such a degree that they create so-called ROH islands. These islands, fixed parts of the genome, could be considered as selection signatures pointing to crucial events in the population history. Indeed, such ROH islands were identified as signatures containing genes with influence on coat colour and body size in Noriker horses (Grilz-Seger et al., 2019). In the case of between breed comparisons, the ROH island based selection signatures might be combined whit other methods, such as F_{ST} analyses. Such approach proved to be useful to show the effect of selection on the chicken genome, revealing signatures for a range of traits of economic interest (Almeida et al., 2019). The ROH islands were also used to analyse Italian pig breeds, shaped by combination of different natural and artificial selection events. The number and frequency of ROH islands varied between breeds, underlining their diversity on metabolic and exterior levels. In some cases, the ROH islands were present only in a single breed, which could be useful information to support conservation programs in local breeds (Schiavo et al., 2020).

1.3 Effective population size

The effective population size (N_e) was first described by (Wright, 1931) based on numbers of males and females. The N_e is defined as the number of individuals of a Wright-Fisher population, in which the amount of genetic drift and inbreeding levels are similar as in the analysed population (Waples, 2016). The Wright-Fisher population is a hypothetical population with finite number of individuals, random mating, without mutation, selection and overlapping generations. It is very similar to the ideal Hardy-Weinberg population except of the population size. The N_e is an important theoretical construct in evolutionary biology, but it has also a practical use in the management of small populations to denote the endangerment status. The general recommendation of the Food and Agricultural organisation of the United Nations (FAO) is to keep the N_e above 50 animals in all cases to minimise the diversity loss. This threshold should also ensure the increase in inbreeding per generation below 1% (Bradley et al., 2004). According to Frankham et al. (2014), the limit of $N_e = 50$ is too low, and it does not suffice to reduce the loss of genetic diversity. According to the suggestions, a N_e >1,000 animals would be required in wild species

to limit the loss in total fitness below 10%. In livestock, the effective population size is usually much lower due to intense artificial selection and increased inbreeding levels. This also means that the economically important livestock species could potentially lose adaptation mechanisms as a result of intense selective breeding. In such populations a permanent diversity monitoring and evaluation procedures should be implemented (Kasarda et al., 2020).

One of the possibilities is to compute N_e based on the increase in inbreeding per generation. The inbreeding levels could be computed from non-genomic data, if pedigree data with sufficient depth and completeness are available. More importantly, the genomic inbreeding coefficient could be computed with ROH, and used for the assessment of the N_e. Another method to estimate N_e is based on LD from a large amount of SNPs. This method was described in Hayes et al. (2003) and Tenesa et al. (2007), considering mutations and finite sample sizes. The LD in short distances on the genome points to N_e in a more distant past, while LD over large distances could be used to estimate recent N_e. The reason for this distinction is the increased probability of recombination over large distances, thus the small segments preserving information on N_e for a longer time. Along these lines Hayes et al. (2003) also provides an exact measure to determine past N_e at specific times. This measure is based on number of generations in the past, based on the genetic distance between two loci. The exact formula is $t = 1/2c$, where the t is the number of generations in the past for which the N_e is computed, and the c is the distance between the two loci. The length of the so-called short and long distances was put into context by Pérez O'Brien et al. (2014), who analysed LD between markers from 0.1 Mb to 10 Mb apart. The average LD values from the 0.1 Mb corresponds to N_e from 2000 generations ago, and the LD from the 10 Mb segments shows the from N_e about 10 generations ago, following the formula of Hayes et al. (2003).

From the historical perspective, in cattle, the N_e was about 3000 at the beginning of Holocene period (about 8 to 12 thousand years before present), just before any domestication processes began. While the N_e is a unique characteristic of each population, low values of N_e are relatively common. In livestock, it has currently decreased to about $N_e \sim 500$, or even less in endangered breeds (Barbato et al., 2015; Deng et al., 2019). A closer look at recent studies on the matter reveals, however, that even the N_e of 500 is rarely reached. These trends were very well represented by a high profile study of the US Holstein population, which despite of the more than 200 thousand studied individuals in the last 29 years, the N_e of the breed was only 58 (Makanjuola et al., 2020). Similarly, small N_e values around 100 were identified in other livestock species, such as in sheep (Granado-Tajada et al., 2020). The N_e was even lower in horses, with N_e = 39 in the Native Italian horse breed (Ablondi et al., 2020). Relatively higher values were found in recent studies of Galway sheep with N_e = 184 (McHugo et al., 2019), Lacone sheep with N_e = 200 (Rodríguez-Ramilo et al., 2019). The decrease of N_e throughout the last 100 generations of two Polish pig breeds was documented by Jasielczuk et al. (2020), when the Złotnicka breed decreased from 147 to only 23, and the Polish Landrace from 263 to 91.

2 Conclusion

In this paper, we review LD, genomic inbreeding and N_e. We show how these population genetics parameters are being used to assess the diversity of populations. Also, we highlight the connections between them, such as the use of inbreeding and LD in computation of N_e. Another common point was the use of both the LD and the so-called ROH islands to estimate selection signatures. The truly unifying point between these analyses is the insight into the population history, however. The distance between loci for which the LD is being computed determines the generations in the past, for which the N_e is being estimated. Such insight into the N_e of the population could range for 10s to 1000s of generations. On the other hand, the inbreeding analyses with ROH look at a much shorter time frame. Based on the commonly used parameter settings, the ROH show common ancestors from 3 to 50 generations in the past. Based on the reviewed literature, we suggest using all three analyses in livestock studies to explore the breeding history of populations on the genomic level.

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References

Ablondi, M. et al. (2020). Genetic Diversity and Signatures of Selection in a Native Italian Horse Breed Based on SNP Data. *Animals*, 10(6), 1005. https://doi.org/10.3390/ani10061005

Almeida, O.A.C. et al. (2019). Identification of selection signatures involved in performance traits in a paternal broiler line. *BMC Genomics*, 20(1), 449.

https://doi.org/10.1186/s12864-019-5811-1

Ardlie, K.G., Kruglyak, L. & Seielstad, M. (2002). Patterns of linkage disequilibrium in the human genome. Nature Reviews Genetics, 3(4), 299–309. https://doi.org/10.1038/nrg777

Baes, C. F. et al. (2019). Symposium review: The genomic architecture of inbreeding: How homozygosity affects health

and performance. *Journal of Dairy Science*, 102(3), 2807–2817. https://doi.org/10.3168/jds.2018-15520

Barbato, M. et al. (2015). SNeP: A tool to estimate trends in recent effective population size trajectories using genome-wide SNP data. *Frontiers in Genetics*, 6. https://doi.org/10.3389/fgene.2015.00109

Bradley, D. et al. (2004). *Secondary guidelines for development of national farm animal genetic resources management plans*. Food and Agricultural Organization of United Nations (FAO), Roma.

Brüniche-Olsen, A. et al. (2018). Runs of homozygosity have utility in mammalian conservation and evolutionary studies. *Conservation Genetics*, 19(6), 1295–1307. https://doi.org/10.1007/s10592-018-1099-y

Ceballos, F. C. et al. (2018). Runs of homozygosity: Windows into population history and trait architecture. *Nature Reviews Genetics*, 19(4), 220–234. https://doi.org/10.1038/nrg.2017.109

Curik, I., Ferenčaković, M. & Sölkner, J. (2017). Genomic dissection of inbreeding depression: A gate to new opportunities. *Revista Brasileira de Zootecnia*, 46(9), 773–782. https://doi.org/10.1590/s1806-92902017000900010

Deng, T. et al. (2019). Genome-Wide SNP Data Revealed the Extent of Linkage Disequilibrium, Persistence of Phase and Effective Population Size in Purebred and Crossbred Buffalo Populations. *Frontiers in Genetics*, 9. https://doi.org/10.3389/fgene.2018.00688

Fariello, M.I. et al. (2017). Accounting for linkage disequilibrium in genome scans for selection without individual genotypes: The local score approach. *Molecular Ecology*, 26(14), 3700–3714. https://doi.org/10.1111/mec.14141

Ferenčaković, M., Sölkner, J. & Curik, I. (2013). Estimating autozygosity from high-throughput information: Effects of SNP density and genotyping errors. *Genetics Selection Evolution*, 45(1), 42. https://doi.org/10.1186/1297-9686-45-42

Frankham, R., Bradshaw, C.J.A. & Brook, B.W. (2014). Genetics in conservation management: Revised recommendations for the 50/500 rules, Red List criteria and population viability analyses. *Biological Conservation*, 170, 56–63. https://doi.org/10.1016/j.biocon.2013.12.036

Gazal, S. (2017). Linkage disequilibrium-dependent architecture of human complex traits shows action of negative selection. *Nature Genetics*, 49(10), 14.

Georges, M., Charlier, C. & Hayes, B. (2019). Harnessing genomic information for livestock improvement. *Nature Reviews Genetics*, 20(3), 135–156. https://doi.org/10.1038/s41576-018-0082-2

Granado-Tajada, I. et al. (2020). Inbreeding, effective population size, and coancestry in the Latxa dairy sheep breed. *Journal of Dairy Science*, 103(6), 5215–5226. https://doi.org/10.3168/jds.2019-17743

Grilz-Seger, G. et al. (2019). Analysis of ROH patterns in the Noriker horse breed reveals signatures of selection for coat color and body size. *Animal Genetics*, 50(4), 334–346. https://doi.org/10.1111/age.12797

Hayes, B. J. et al. (2003). Novel Multilocus Measure of Linkage Disequilibrium to Estimate Past Effective Population Size. *Genome Research*, 13(4), 635–643. https://doi.org/10.1101/gr.387103

Hickey, J. M. et al. (2017). Genomic prediction unifies animal and plant breeding programs to form platforms for biological discovery. *Nature Genetics*, 49(9), 1297–1303. https://doi.org/10.1038/ng.3920

Hill, W.G. & Robertson, A. (1968). Linkage disequilibrium in finite populations. *TAG. Theoretical and Applied Genetics. Theoretische Und Angewandte Genetik*, 38(6), 226–231. https://doi.org/10.1007/BF01245622

Jasielczuk, I. et al. (2020). Comparison of linkage disequilibrium, effective population size and haplotype blocks in Polish Landrace and Polish native pig populations. *Livestock Science*, 231, 103887. https://doi.org/10.1016/j.livsci.2019.103887

Karimi, K., Esmailizadeh Koshkoiyeh, A. & Gondro, C. (2015). Comparison of linkage disequilibrium levels in Iranian indigenous cattle using whole genome SNPs data. *Journal of Animal Science and Technology*, 57. https://doi.org/10.1186/s40781-015-0080-2

Kasarda, R. et al. (2015). Genome-wide selection signatures in Pinzgau cattle. *Potravinarstvo Slovak Journal of Food Sciences*, 9(1), 268–274. https://doi.org/10.5219/478

Kasarda, R., Jamborová, Ľ. & Moravčíková N. (2020). Genetic diversity and production potential of animal food resources. *Acta fytotechnica et zootechnica*, 23(2), 102–108. https://doi.org/10.15414/afz.2020.23.02.102-108

Khatkar, M. S. et al. (2008). Extent of genome-wide linkage disequilibrium in Australian Holstein-Friesian cattle based on a high-density SNP panel. *BMC Genomics*, 9(1), 187. https://doi.org/10.1186/1471-2164-9-187

Kijas, J. W. et al. (2014). Linkage disequilibrium over short physical distances measured in sheep using a high-density SNP chip. *Animal Genetics*, 45(5), 754–757. https://doi.org/10.1111/age.12197

Kim, E.-S. et al. (2013). Effect of Artificial Selection on Runs of Homozygosity in U.S. Holstein Cattle. *PLoS ONE*, 8(11), e80813. https://doi.org/10.1371/journal.pone.0080813

Lu, D. et al. (2012). Linkage disequilibrium in Angus, Charolais, and Crossbred beef cattle. *Frontiers in Genetics,* 3. https://doi.org/10.3389/fgene.2012.00152

Makanjuola, B.O. et al. (2020). Effect of genomic selection on rate of inbreeding and coancestry and effective population size of Holstein and Jersey cattle populations. *Journal of Dairy Science*, 103(6), 5183–5199. https://doi.org/10.3168/jds.2019-18013

Mastrangelo, S. et al. (2014). Genome wide linkage disequilibrium and genetic structure in Sicilian dairy sheep breeds. *BMC Genetics*, 15(1), 108. https://doi.org/10.1186/s12863-014-0108-5

McHugo, G.P. et al. (2019). A Population Genomics Analysis of the Native Irish Galway Sheep Breed. *Frontiers in Genetics*, 10. https://doi.org/10.3389/fgene.2019.00927

McKay, S.D. et al. (2007). Whole genome linkage disequilibrium maps in cattle. *BMC Genetics*, 8(1), 74. https://doi.org/10.1186/1471-2156-8-74

McQuillan, R. et al. (2008). Runs of Homozygosity in European Populations. *The American Journal of Human Genetics*, 83(3), 359–372. https://doi.org/10.1016/j.ajhg.2008.08.007

Meuwissen, T.H.E., Hayes, B.J. & Goddard, M.E. (2001). Prediction of Total Genetic Value Using Genome-Wide Dense Marker Maps. *Genetics*, 157(4), 1819–1829.

Mills, M.C. & Rahal, C. (2019). A scientometric review of genome-wide association studies. *Communications Biology,* 2(1), 1–11. https://doi.org/10.1038/s42003-018-0261-x

Moravčíková, N. et al. (2019). Analysis of selection signatures in the beef cattle genome. *Czech Journal of Animal Science*, 64(12), 491–503. https://doi.org/10.17221/226/2019-CJAS

Moravčíková, N. & Kasarda, R. (2020). Use of High-density SNP analyses to develop a long-term strategy for conventional populations to prevent loss of diversity – review. *Acta fytotechnica et zootechnica,* 23(4), 236–240. https://doi.org/10.15414/afz.2020.23.04.236-240

Otto, S.P. (2000). Detecting the form of selection from DNA sequence data. *Trends in Genetics,* 16(12), 526–529. https://doi.org/10.1016/S0168-9525(00)02141-7

Pérez O'Brien, A.M. et al. (2014). Linkage disequilibrium levels in Bos indicus and Bos taurus cattle using medium and high density SNP chip data and different minor allele frequency distributions. *Livestock Science,* 166, 121–132. https://doi.org/10.1016/j.livsci.2014.05.007

Peripolli, E. et al. (2016). Runs of homozygosity: Current knowledge and applications in livestock. *Animal Genetics*. https://doi.org/10.1111/age.12526

Porto-Neto, L.R., Kijas, J.W. & Reverter, A. (2014). The extent of linkage disequilibrium in beef cattle breeds using high-density SNP genotypes. *Genetics, Selection, Evolution: GSE*, 46, 22. https://doi.org/10.1186/1297-9686-46-22

Qanbari, S. (2020). On the Extent of Linkage Disequilibrium in the Genome of Farm Animals. *Frontiers in Genetics*, 10. https://doi.org/10.3389/fgene.2019.01304

Rebelato, A.B. & Caetano, A.R. (2018). Runs of homozygosity for autozygosity estimation and genomic analysis in production animals. *Pesquisa Agropecuária Brasileira*, 53(9), 975–984. https://doi.org/10.1590/s0100-204x2018000900001

Reich, D.E. et al. (2001). Linkage disequilibrium in the human genome. *Nature*, 411(6834), 199–204. https://doi.org/10.1038/35075590

Rodríguez-Ramilo, S.T., Elsen, J.M. & Legarra, A. (2019). Inbreeding and effective population size in French dairy sheep: Comparison between genomic and pedigree estimates. *Journal of Dairy Science*, 102(5), 4227–4237. https://doi.org/10.3168/jds.2018-15405

Sabeti, P.C. et al. (2002). Detecting recent positive selection in the human genome from haplotype structure. *Nature*, 419(6909), 832–837. https://doi.org/10.1038/nature01140

Saravanan, K.A. et al. (2020). Selection signatures in livestock genome: A review of concepts, approaches and applications. *Livestock Science*, 241, 104257. https://doi.org/10.1016/j.livsci.2020.104257

Schiavo, G. et al. (2020). Runs of homozygosity islands in Italian cosmopolitan and autochthonous pig breeds identify selection signatures in the porcine genome. *Livestock Science*, 240, 104219. https://doi.org/10.1016/j.livsci.2020.104219

Schmid, M. & Bennewitz, J. (2017). Invited review: Genome-wide association analysis for quantitative traits in livestock – a selective review of statistical models and experimental designs. *Archives Animal Breeding*, 60(3), 335–346. https://doi.org/10.5194/aab-60-335-2017

Signer-Hasler, H. et al. (2019). Runs of homozygosity and signatures of selection: A comparison among eight local Swiss sheep breeds. *Animal Genetics,* 50(5), 512–525. https://doi.org/10.1111/age.12828

Sved, J.A. & Hill, W.G. (2018). One Hundred Years of Linkage Disequilibrium. *Genetics*, 209(3), 629–636. https://doi.org/10.1534/genetics.118.300642

Tam, V. et al. (2019). Benefits and limitations of genome-wide association studies. *Nature Reviews Genetics*, 20(8), 467–484. https://doi.org/10.1038/s41576-019-0127-1

Tenesa, A. et al. (2007). Recent human effective population size estimated from linkage disequilibrium. *Genome Research*, 17(4), 520–526. https://doi.org/10.1101/gr.6023607

Uimari, P. & Tapio, M. (2011). Extent of linkage disequilibrium and effective population size in Finnish Landrace and Finnish Yorkshire pig breeds. *Journal of Animal Science*, 89(3), 609–614. https://doi.org/10.2527/jas.2010-3249

Utsunomiya, Y.T. et al. (2013). Detecting Loci under Recent Positive Selection in Dairy and Beef Cattle by Combining Different Genome-Wide Scan Methods. *PLOS ONE*, 8(5), e64280. https://doi.org/10.1371/journal.pone.0064280

Voight, B.F. et al. (2006). A Map of Recent Positive Selection in the Human Genome. *PLOS Biology*, 4(3), e72. https://doi.org/10.1371/journal.pbio.0040072

Waples, R.S. (2016). Making sense of genetic estimates of effective population size. *Molecular Ecology*, 25(19), 4689–4691. https://doi.org/10.1111/mec.13814

Wright, S. (1931). Evolution in Mendelian Populations. *Genetics*, 16(2), 97–159.

