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Runs of homozygosity: current knowledge and applications in livestock

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Summary

This review presents a broader approach to the implementation and study of runs of homozygosity (ROH) in animal populations, focusing on identifying and characterizing ROH and their practical implications. ROH are continuous homozygous segments that are common in individuals and populations. The ability of these homozygous segments to give insight into a population's genetic events makes them a useful tool that can provide information about the demographic evolution of a population over time. Furthermore, ROH provide useful information about the genetic relatedness among individuals, helping to minimize the inbreeding rate and also helping to expose deleterious variants in the genome. The frequency, size and distribution of ROH in the genome are influenced by factors such as natural and artificial selection, recombination, linkage disequilibrium, population structure, mutation rate and inbreeding level. Calculating the inbreeding coefficient from molecular information from ROH (F_{ROH}) is more accurate for estimating autozygosity and for detecting both past and more recent inbreeding effects than are estimates from pedigree data (F_{PED}). The better results of F_{ROH} suggest that F_{ROH} can be used to infer information about the history and inbreeding levels of a population in the absence of genealogical information. The selection of superior animals has produced large phenotypic changes and has reshaped the ROH patterns in various regions of the genome. Additionally, selection increases homozygosity around the target locus, and deleterious variants are seen to occur more frequently in ROH regions. Studies involving ROH are increasingly common and provide valuable information about how the genome's architecture can disclose a population's genetic background. By revealing the molecular changes in populations over time, genome-wide information is crucial to understanding antecedent genome architecture and, therefore, to maintaining diversity and fitness in endangered livestock breeds.

Keywords autozygosity, genetic diversity, homozygosity, inbreeding, livestock

Introduction

In diploid genomes, runs of homozygosity (ROH) are continuous homozygous segments of the DNA sequence (Gibson *et al.* 2006). ROH have been applied to quantifying individual autozygosity (McQuillan *et al.* 2008; Ferenčaković *et al.* 2011, 2013a; Keller *et al.* 2011; Silió *et al.* 2013; Marras *et al.* 2014; Zavarez *et al.* 2015), given their high correlation with autozygosity ($r \approx 0.7$) (McQuillan *et al.* 2008) and, consequently, the high accuracy with which autozygosity is detected (Keller *et al.* 2011). Autozygosity occurs when parents have a common ancestor and pass shared chromosomal segments on to their progeny, i.e. an individual inherits chromosomal fragments that are identical by descent (IBD) from both parents (Wright 1922), resulting in homozygous segments in the offspring's genome that give rise to ROH (Broman & Weber 1999). This results from population phenomena such as genetic drift, population bottleneck, inbreeding and intensive artificial selection (Falconer & Mackay 1996).

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The identification and characterization of ROH can provide insight into how population history, structure and demography have evolved over time. Such population phenomena can impact homozygosity patterns in the genome, and these events can be revealed by ROH (Bosse *et al.* 2012; Purfield *et al.* 2012; Herrero-Medrano *et al.* 2013). ROH can identify inbreeding levels and the genetic relationships between individuals, providing support in estimating the true level of autozygosity at the individual and population levels (Ferenčaković *et al.* 2011, 2013a; Kim *et al.* 2015a; Zavarez *et al.* 2015). Selection pressure and mating schemes can also be revealed by ROH (Bosse *et al.* 2012; Purfield *et al.* 2012; Karimi 2013; Kim *et al.* 2013; Zhang *et al.* 2015).

The use of high-density SNP arrays in scanning the genome for ROH has been proposed as an effective method for identifying IBD haplotypes (Gibson *et al.* 2006; Lencz *et al.* 2007). In this regard, SNP arrays can provide information about both past and more recent demographic variations of a population, i.e. population size reflecting founder effects and bottlenecks (Megens *et al.* 2009; Bosse *et al.* 2012), allowing a comparison of the degree of homozygosity among populations with varying degrees of isolation and inbreeding (Kirin *et al.* 2010). Curik *et al.* (2014) presented a review of different approaches to estimate inbreeding levels using genomic information, highlighting the importance of ROH in quantifying and understanding inbreeding in livestock, humans and plants.

The intense selection in livestock has alerted the scientific community to the necessity of strategies to preserve populations (Herrero-Medrano *et al.* 2013), characterize and monitor autozygosity, and maintain genetic diversity in long-term animal breeding programs (De Cara *et al.* 2013; Bosse *et al.* 2015). Studies have also shown a relationship between ROH in the genome and the occurrence of recessive disorders, mainly in humans (Lencz *et al.* 2007; Nalls *et al.* 2009; Vine *et al.* 2009; Szpiech *et al.* 2013) and more recently in livestock (Biscarini *et al.* 2014a; Kim *et al.* 2015a; Mészáros *et al.* 2015; Muchadeyi *et al.* 2015; Zhang *et al.* 2015). The analysis of ROH has therefore proved to be important in the design of mating systems to minimize the inbreeding rate (Toro & Varona 2010; Biscarini *et al.* 2015a). Moreover, it is important in mapping recessive alleles related to the occurrence of diseases, as ROH have an increased risk of carrying IBD deleterious recessive alleles, thereby reducing the viability of the organism (De Cara *et al.* 2013; Bosse *et al.* 2015).

Our review presents a broad overview of the study and application of ROH in animal populations and future prospective research areas. The addressed aspects are related to: (i) a brief history of research on ROH, including the first studies on ROH in different livestock species; (ii) practical implications of ROH identification, in which we discuss the software used to identify ROH and the consequences of some of the selected parameters when detecting them; (iii) identification and characterization of ROH in livestock populations, wherein ROH patterns and their relationship with demographic history and inbreeding are identified; (iv) the impact of molecular information on the measure of inbreeding coefficients; (v) the effect on phenotype and disease risk, exploring autozygosity throughout the genome to determine whether ROH are correlated to deleterious variants; (vi) the effects of selection on ROH; (vii) genetic diversity and ROH, exploring genomic tools to minimize the loss of genetic diversity in livestock populations; and (viii) a final discussion to recognize trends in livestock ROH studies and gaps for new research areas.

A brief history of the surge of ROH research

The first human study that recognized long homozygous chromosomal segments was conducted by Broman & Weber (1999). They inferred that long chromosomal segments likely represent autozygosity and may have implications for human health. The first human study using high-density SNP arrays was conducted by Gibson *et al.* (2006), whose results described different ROH lengths, frequency and distribution across the genome. This work spurred a host of other research on ROH analysis in human population genetics (McQuillan *et al.* 2008; Kirin *et al.* 2010; Nothnagel *et al.* 2010). In livestock, the first studies on ROH were conducted on cattle by Sölkner *et al.* (2010) and Ferenčaković *et al.* (2011). Several studies on ROH in cattle followed (Purfield *et al.* 2012; Bjelland *et al.* 2013; Ferenčaković *et al.* 2013a; Kim *et al.* 2013). In swine, the first studies on ROH were conducted to highlight the influence of population relationships, demographic history and the effects of inbreeding on homozygosity (Bosse *et al.* 2012; Herrero-Medrano *et al.* 2013). Silió *et al.* (2013) and Saura *et al.* (2015) measured inbreeding and inbreeding depression in pigs from pedigree and genome-wide data. Khanshour (2013a) and Metzger *et al.* (2015) performed ROH analysis to reveal signatures of positive selection in horses. In sheep, research on population history and structure, and homozygosity using ROH was presented by Beynon *et al.* (2015) and Muchadeyi *et al.* (2015). Guangul (2014) characterized ROH patterns and genomic inbreeding coefficients in goats.

Criteria and software for detecting ROH

To date, few studies have examined and compared the performance of different software to identify ROH and which set of parameters within a given software is optimal for detecting them (Howrigan *et al.* 2011). Different studies have used different methodologies for predicting ROH (Zhang *et al.* 2013). A recurrent limitation in studies involving ROH is the lack of consensus in establishing the criteria to define ROH (Ku *et al.* 2011). The main objective in establishing criteria for defining the patterns of ROH lies

in the fact that they are used to identify the autozygosity, differentiating non-autozygotic segments that are identical by state from autozygotic and IBD segments.

Howrigan *et al.* (2011) evaluated the performance of three major software programs, PLINK (Purcell *et al.* 2007), GERMLINE (Gusev *et al.* 2009) and BEAGLE (Browning & Browning 2010). The authors observed that PLINK generated the highest proportion of significant results to detect autozygosity from distant common ancestors, outperforming the other two programs. GERMLINE, compared to PLINK, underperformed regarding the proportion of significant results to detect autozygosity due to the low resolution at the start and endpoints of ROH. The authors had hypothesized that BEAGLE would yield the best accuracy in detecting autozygosity because it incorporated linkage disequilibrium (LD), but that was not observed.

Karimi (2013) analyzed PLINK (Purcell *et al.* 2007), SVS (Golden Helix SNP & Variation Suite v.7.6.8) and CGATOH (Zhang *et al.* 2013) to determine whether frequencies of detected ROH were significantly different. PLINK and SVS are common tools used to identify ROH patterns, whereas CGATOH is a new algorithm proposed by Zhang *et al.* (2013). The results of the three programs showed that the ROH islands were located in similar regions with only small differences in the frequency of ROH. However, CGATOH captured a higher number of individuals that had ROH compared to the other two. The SVS and PLINK results overlapped to a larger extent when compared to CGATOH. The frequency of ROH were significantly different ($P < 0.001$), but all three software identified ROH islands in similar regions. The development of accurate tools to assess genome-wide autozygosity is a prerequisite for successful research on ROH (Ku *et al.* 2011). In this sense, new algorithms and studies have also been developed to assess and compare individual genome-wide homozygosity (Seelow *et al.* 2009; Browning & Browning 2010; Polašek *et al.* 2010; Marras *et al.* 2016).

The inconsistency among the criteria for defining ROH make it difficult to compare studies, because the lack of consensus allows different thresholds across studies (Howrigan *et al.* 2011; Ku *et al.* 2011). This limitation may be responsible for bias in ROH-based estimates of autozygosity (Ferenčaković *et al.* 2013b). Some of the major works on ROH for various livestock species and the respective parameters and thresholds used to identify ROH are presented in Table 1. It can be seen that the criteria for identification and characterization of ROH differ among and within species.

Howrigan *et al.* (2011) reported that some parameters and thresholds imposed during sequence analysis can impact the number and length of ROH. Results from Mastrangelo *et al.* (2016) showed different inbreeding coefficient estimates from ROH (F_{ROH}) depending on whether one, two or three heterozygous genotypes were allowed. Ferenčaković *et al.* (2013b) pointed out that the density of the SNP chip used to generate the data for ROH analysis, and also the frequency of SNP genotyping errors, can influence ROH identification in cattle. The 50 K panel overestimated the number of small segments (1–4 Mb long). With the HD panel, the number of segments longer than 8 Mb was underestimated when limiting the number of heterozygous SNP genotypes within a single ROH. The same was observed by Purfield *et al.* (2012), whose findings pointed out that the 50 K panel was appropriate for identifying ROH longer than 5 Mb. The minimum ROH length that can be detected depends therefore on the density of the SNP chip. In addition, allowing a number of genotyping errors in long ROH may minimize the underestimation of these segments (Ferenčaković *et al.* 2013b).

Given that the definition of ROH is still not unambiguous and that some studies employ more strict criteria compared to others (Ku *et al.* 2011), we believe that the lack of standards for ROH increases the likelihood of biased and false-positive results, because one set of parameters can be chosen among many. Therefore, to overcome this situation, we suggest a cautious and critical interpretation when comparing studies, analyzing the density of the SNP chip used, the minimum length of ROH, the number of genotyping errors allowed and the minimum number of SNPs allowed in a single ROH, as they are likely to greatly affect ROH-based estimates of autozygosity. Furthermore, additional studies identifying which set of parameters is optimal for detecting ROH is needed in a wider range of livestock species, given that it has not been systematically analyzed and the published works are mainly in cattle.

Additionally, several factors can influence the frequency, size and location of ROH in individuals. These factors may be related to recombination, LD and mutation rate (Gibson *et al.* 2006). Other factors may be derived from chromosomal aberrations such as the occurrence of uniparental disomy (inheritance of a pair of homologous chromosomes from only one parent), hemizygous deletion (one chromosome is deleted and is not repaired, resulting in the loss of half genome for a locus) or loss of heterozygosity in the genome (the inactivation of a functional allele at a heterozygous locus) (Engel 1980; Koufos *et al.* 1985; Yokota *et al.* 1987; Dong 2001; Huie *et al.* 2002; Marguerite *et al.* 2008).

Purfield *et al.* (2012) observed in cattle that 87.2% of the animals in the dataset had a ROH located on chromosome 14 (centered on the 25-Mb position). This ROH was 127.3 kb long and consisted of 28 SNPs. When analyzed using HAPLOVIEW (Barret *et al.*, 2005), they observed that most of the SNPs in this region were in high LD with each other. Bosse *et al.* (2012) studied pigs and observed that longer ROH were located in regions of low recombination in the central part of the chromosome and that smaller ROH had a relatively higher distribution toward telomeric regions. Herrero-Medrano *et al.* (2013) also reported a correlation among LD, ROH size and recombination rate in

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Table 1 Comparison of pre-set parameters for identification and characterization of ROH in different animal species.

Author	Species	Software	SNP array	Consecutive SNPs/ROH[1]	Density[2] (SNP/kb)	Maximum gap[3] (kb)	Minimum length[4] (kb)	Heterozygous SNP/sliding window	Missing SNP/sliding window
Ferenčaković *et al.* (2011)	Cattle: dual purpose	FORTRAN 90	Illumina Bovine SNP 50 K BeadChip	15	–	–	1000	00	–
Purfield *et al.* (2012)	Cattle: beef, dairy and dual purpose[5]	PLINK v1.07	Illumina BovineHD Genotyping BeadChip assay	58	1/50	100	500	01	02
Purfield *et al.* (2012)	Cattle: beef, dairy and dual purpose[5]	PLINK v1.07	Illumina Bovine SNP 50 K BeadChip	No restriction	1/120	1000	500	01	02
Bjelland *et al.* (2013)	Cattle: dairy	PLINK v1.07	Illumina Bovine SNP 50 K BeadChip	30	–	–	–	00	01
Ferenčaković *et al.* (2013a)	Cattle: dairy and dual purpose[5]	SNP & VARIATION SUITE v7.6.8	Illumina Bovine SNP 50 K BeadChip	15	1/1000	1000	1000	00	05
Karimi (2013)	Cattle: beef, dairy and dual purpose[5]	SNP & VARIATION SUITE v7.6.8 PLINK v1.07 CGATOH	Illumina BovineHD Genotyping BeadChip assay	30	1/50	250	1000	01	04
Biscarini *et al.* (2014a)	Cattle: dairy	PLINK v1.07	Illumina Bovine SNP 50 K Beadchip	No restriction	–	1000	–	01	05
Marras *et al.* (2014)	Cattle: beef, dairy and dual purpose[5]	SAS 9.2 script (SAS Institute 2012)	Illumina bovine SNP 50 K BeadChip	15	–	1000	1000	00	00
Scraggs *et al.* (2014)	Cattle: beef	PLINK v1.07	Illumina bovine SNP 50 K BeadChip	50	–	–	1000	01	01
Mészáros *et al.* (2015)	Cattle: dual purpose	–	Illumina Bovine SNP 50 K BeadChip	30	–	–	1000	00	00
Williams *et al.* (2015)	Cattle: kept for conservation	R Development Core Team (2008)	Illumina BovineHD Genotyping BeadChip assay	–	1/50	100	100	01	02
Zavarez *et al.* (2015)	Cattle: beef	SNP & VARIATION SUITE v7.6.8	Illumina BovineHD Genotyping BeadChip assay	30	1/100	500	4000	02 (ROH $\geq$ 4 Mb)	05
Zavarez *et al.* (2015)	Cattle: beef	SNP & VARIATION SUITE v7.6.8	Illumina BovineHD Genotyping BeadChip assay	30	1/100	500	500	00 (ROH $<$ 4 Mb)	05
Bosse *et al.* (2012)	Swine	PLINK v1.07	Porcine SNP60 Beadchip	20	1/1000	–	10	01	–
Ai *et al.* (2013)	Swine	PLINK v1.07	Porcine SNP60 Beadchip	–	–	–	500	01	05
Herrero-Medrano *et al.* (2013)	Swine	PLINK v1.07	Porcine SNP60 Beadchip	20	1/1000	1000	10	01	–
Silió *et al.* (2013)	Swine	SNP & VARIATION SUITE v7.6.8	Porcine SNP60 Beadchip	30	1/100	1000	1000	–	02
Saura *et al.* (2015)	Swine	FORTRAN	Porcine SNP60 Beadchip	30	1/100	1000	–	01	02
Zhang *et al.* (2014)	Swine	PLINK v1.07	Porcine SNP60 Beadchip	10	1/500	1000	5000	–	01
Traspov *et al.* (2016)	Swine	PLINK v1.09	Porcine SNP60 Beadchip	–	–	–	500	01	05
Khanshour (2013a)	Horse	PLINK v1.07	Equine SNP50 BeadChip	50	1/50	1000	500	–	–

Table 1 (Continued)

Author	Species	Software	SNP array	Consecutive SNPs/ROH[1]	Density[2] (SNP/kb)	Maximum gap[3] (kb)	Minimum length[4] (kb)	Heterozygous SNP/sliding window	Missing SNP/sliding window
Al-Mamun *et al.* (2015)	Sheep	PLINK v1.07	Illumina Ovine SNP50 BeadChip	–	–	250	500	01	02
Muchadeyi *et al.* (2015)	Sheep	PLINK v1.07	Illumina Ovine SNP50 Beadchip	20	1/50	500	–	00	02
Guangul (2014)	Goat	CGATOH	47 K SNP bead chip	20	–	1000	1000	01	05

ROH, runs of homozygosity; '–', information not available.
[1]Minimum number of consecutive SNPs needed to define a segment as a ROH.
[2]Minimum allowed density of SNPs inside a run.
[3]Maximum gap between consecutive homozygous SNPs.
[4]Minimum length to define a ROH.
[5]Papers analyzing different breeds, and each breed with a different purpose.

pigs. The authors found a positive correlation between average values of LD and number of ROH per chromosome ($\rho = 0.70$, $P < 0.002$) and a negative correlation between ROH size and rate of recombination ($\rho = -0.67$, $P < 0.003$). Ai *et al.* (2013) compared Chinese and Western pig populations and observed that the Chinese population of Jinhua pigs had the highest fraction of long ROH and hence a high LD rate. As expected by the authors, Chinese pig populations that had lower LD exhibited fewer ROH.

ROH in livestock populations

After the first pioneering work by Sölkner *et al.* (2010), scientists studied ROH more deeply in various livestock species, focusing on their identification and characterization and on the relationship with demographic history and inbreeding.

Purfield *et al.* (2012) analyzed the patterns of ROH in *Bos taurus* cattle and observed that they differed markedly among breeds. For almost all breeds, most ROH were short (1–5 Mb). Holstein, Holstein-Friesian and Friesian breeds showed the greatest coverage in the longer ROH. The three most homozygous animals had an average of 700.3 Mb of their genome as ROH. Kim *et al.* (2013) studied Holstein cattle with different selection intensities and observed that the mean ROH length per animal was ≈6 Mb (Table 2). ROH shorter than 5 Mb accounted for 53% of all segments identified and contributed less than 30% of the total cumulative ROH length. The ROH distribution pattern observed in Holstein cows can result from population bottlenecks during the breed formation together with a constant directional selection, resulting in high inbreeding. In this same study, non-selected animals showed a significantly lower average size of ROH.

Ferenčaković *et al.* (2013a) studied the autozygosity in Brown Swiss, Fleckvieh, Norwegian Red and Tyrol Grey cattle breeds and found that distribution and frequencies of ROH varies among breeds. Brown Swiss animals had the highest average number of ROH (98.9) and the highest genome coverage with ROH (Table 2). The shortest average ROH length was found in Fleckvieh animals, whose genome was composed mostly of many short ROH. Brown Swiss animals had mostly few large ROH. Norwegian Red animals showed a similar pattern as Fleckvieh, and some Tyrol Grey animals had few ROH that, however, covered more than 630 Mb of the genome. According to the authors, the high number of long ROH observed in Brown Swiss animals is related to the importation of semen from a small number of bulls (Yoder & Lush 1937). Fleckvieh animals showed a small autozygous proportion of the genome, consistent with a larger effective population size. The ROH patterns found in Norwegian Red animals is attributed to a high heterogeneity that has resulted from the historic admixture in the breed (Ferenčaković *et al.* 2013a).

Table 2 Comparison between the mean of the total number of ROH, the mean genome length covered by ROH (Mb), and the mean genome proportion covered by ROH (%) in different livestock species.

Author	Species	SNP array	Breed/population	*n*	Average number of ROH	Mean genome length covered by ROH (Mb)	Mean genome proportion covered by ROH (%)	Mean ROH length (Mb)
Purfield *et al.* (2012)	Cattle	Illumina BovineHD Genotyping BeadChip	Angus	39	–	198.60[1]	7.91[2]	5.09[1]
			Hereford	40	–	198.70[1]	7.91[2]	4.96[1]
			Belgian Blue	38	–			2.12–2.46[3]
			Charolais	117	–			0.68–0.79[3]
			Friesian	98	–			0.89–0.95[3]
			Holstein	262	–	80.58–93.48[1]	3.20–3.72[2]	0.30–0.35[3]
			Holstein-Friesian crosses	111	–			0.72–0.84[3]
			Limousin	128	–			0.63–0.73[3]
			Simmental	58	–			1.39–1.61[3]
Ferenčaković *et al.* (2013a)	Cattle	Illumina Bovine SNP 50 K BeadChip	Brown Swiss	304	98.9	396.80	15.60[4]	1.30[1]
			Fleckvieh	502	94.5	223.10	8.77[4]	0.44[1]
			Norwegian Red	498	80.0	253.50	9.96[4]	0.51[1]
			Tyrol Grey	117	72.3	221.00	8.68[4]	1.88[1]
Kim *et al.* (2013)	Cattle	Illumina Bovine SNP 50 K BeadChip	Unselected line	299	31.1[5]/13.5[6]	–	–	6.61[5]/10.0[6]
			Contemporary Holsteins	1634	43.5[5]/20.1[6]	–	–	
			Selected line for milk production	151	40.4[5]/19.5[6]	–	–	
Marras *et al.* (2014)	Cattle	Illumina bovine SNP 50 K BeadChip	Italian Holstein	2093	81.7	297.00	11.61[7]	3.6
			Italian Brown	749	94.6	371.00	14.51[7]	3.9
			Piedmontese	364	54.0	106.00	4.14[7]	1.9
			Marchigiana	410	71.4	210.00	8.21[7]	–
			Italian Simmental	479	94.3	210.00	8.21[7]	2.2
Zavarez *et al.* (2015)	Cattle	Illumina BovineHD Genotyping BeadChip	Nellore	1278	–	120.22[8]	4.79	1.26
Bosse *et al.* (2012)	Swine	Porcine SNP60 BeadChip	European pig breeds European wild boar Asian wild boars Chinese pigs	52	778.8	645.95[9]	23.00	1.11
Herrero-Medrano *et al.* (2013)	Swine	Porcine SNP60 BeadChip	Chato Murciano	25	34	814.47[9]	29.00	23.95[3]
			Bisaro	15	13	280.85[9]	10.00	21.60[3]
			Wild boars	18	30	<561.70[9]	<20.00	<18.72[3]
			Iberian	31	26	<561.70[9]	<20.00	<21.60[3]
			Manchado de Jabugo	08	24	<561.70[9]	<20.00	<23.40
Traspov *et al.* (2016)	Swine	Porcine SNP60 BeadChip	Russia, Belorussia, Kazakhstan and Ukraine breeds	170	–	72.30	2.57[9]	0.42[3]
			Chinese breeds	135	–	106.00	3.77[9]	0.78[3]
			International commercial breeds	153	–	123.28	4.38[9]	0.80[3]

Table 2 (Continued)

Author	Species	SNP array	Breed/population	*n*	Average number of ROH	Mean genome length covered by ROH (Mb)	Mean genome proportion covered by ROH (%)	Mean ROH length (Mb)
Metzger *et al.* (2015)	Horse	Illumina SNP50 BeadChip	Sorraia	02	4175[5]	798.63	35.60[10]	0.19[3]
			Dülmen Horse	01	2804[5]	416.55	18.57[10]	0.14[3]
			Arabian	01	3581[5]	565.57	25.21[10]	0.15[3]
			Saxon-Thuringian Heavy Warmblood	01	3138[5]	476.06	21.22[10]	0.15[3]
			Thoroughbred	01	4595[5]	953.19	42.49[10]	0.20[3]
			Hanoverian	04	311[5]	454.02	20.24[10]	0.14[3]
Al-Mamun *et al.* (2015)	Sheep	Illumina OvineSNP50 BeadChip	Border Leicester (BL)	253	49.65	–	–	–
			Merino (MER)	265	7.57	–	–	–
			Poll Dorset (PD)	264	37.89	–	–	–
			MER × BL	260	0.30	–	–	–
			MER × BL × PD	231	1.43	–	–	–
Muchadeyi *et al.* (2015)	Sheep	Illumina OvineSNP50 BeadChip	White-vital	41	214	–	–	1.66
			White subvital	16	84	–	–	1.61
			Black	15	72	–	–	1.56
			Grey	22	109	–	–	1.75
Guangul (2014)	Goat	47 K SNP BeadChip	Abergelle	–	33.24	69.11	2.87[11]	2.07[3]
			Western Lowland	–	29.35	63.86	2.65[11]	2.17[3]
			Red Sokoto	–	28.49	115.02	4.78[11]	4.03[3]
			Western African Dwarf	–	42.48	120.17	5.00[11]	2.82[3]
			Sahel	–	21.86	61.68	2.56[11]	2.82[3]

ROH, runs of homozygosity; '–', information not available.
[1]Value defined using the parameters set for the HD panel genotypes.
[2]An estimation considering the overall length of the genome covered by SNPs to be 2510.61 Mb.
[3]Estimation of the mean ROH length (Mb) calculated by dividing the mean genome length covered by ROH (Mb) by the mean of the total number of ROH.
[4]An estimation considering the overall length of the genome covered by SNPs to be 2543.17 Mb.
[5]Values defined using a 50 SNP sliding window.
[6]Values defined using a 100 SNP sliding window.
[7]An estimation considering the overall length of the genome covered by SNPs to be 2556.00 Mb.
[8]An estimation considering the overall length of the genome covered by SNPs to be 2510.00 Mb.
[9]An estimation considering the overall length of the genome covered by SNPs to be 2808.52, based on refseq database Scrofa 10.2, 2014.
[10]An estimation considering the overall length of the genome covered by SNPs to be 2242.87 Mb.
[11]An estimation considering the overall length of the genome covered by SNPs to be 2402.62 Mb.

An example of an extremely homozygous population is Chillingham cattle. The Chillingham breed has not been subjected to selection and for the last 350 years has not experienced migration events and has remained closed (Hall & Hall 1988; Hall *et al.* 2005). Williams *et al.* (2015) observed that 90.9% of the SNPs were monomorphic and that the ROH genome coverage was 95%, indicating a reduced genetic variation and extreme homozygosity in this population.

Bosse *et al.* (2012) examined different European and Asian pig populations and found that ROH size and abundance in the genome varied considerably among individuals from different populations and subpopulations. Moreover, animals of the same population showed similar ROH patterns in their genomes. On average, 23% of the genome was considered to be in ROH, and the most autozygous individual was a Japanese wild boar (78% of its genome). Overall, small ROH were abundant throughout the genome, and even though large ROH were at most one tenth as abundant as small ROH, they still covered a higher proportion of the genome. In domesticated Asian pigs, the cumulative ROH length was dominated by large ROH, which may be indicative of a recently reduced population that originated from a larger population. The genome of the European wild pig had the greatest number of ROH and the highest genome autozygotic proportion. These results are consistent with the evidence of a greater intensity of population bottlenecks due to glaciation in Europe as compared to Asia (Groenen *et al.* 2012). Therefore, further degradation of genetic diversity is expected in European populations as compared to Asian populations.

Herrero-Medrano *et al.* (2013) studied populations of wild and domesticated pigs of the Iberian Peninsula and observed ROH in all animals analyzed. These authors reported differences between wild and domesticated populations in terms of quantity and variation of ROH length. Domesticated pigs had both the highest and lowest average proportion of the genome covered by ROH: 29% in the Chato Murciano breed and 10% in the Bisaro breed. Additionally, Chato Murciano pigs had the highest number of long ROH, emphasizing the recent inbreeding and low genetic diversity in the genome of this breed. The analyses also showed that wild pigs have a very large number of short ROH and no long ROH, which can be correlated with a reduced population size in the past and little inbreeding in recent times (Kirin *et al.* 2010). This pattern of ROH could be from population bottlenecks in the past century in Europe (Apollonio *et al.* 1988), resulting in a drastic reduction of the effective population size. Other possibilities are the formation of sub-populations and the migration of animals, random crossing with domesticated pigs and the absence of geographical barriers in the Iberian Peninsula, which may have prevented high inbreeding in wild pigs (Ferreira *et al.* 2009).

Metzger *et al.* (2015) identified ROH in 10 horses of six different populations to estimate the genetic diversity and detect signatures of selection. Small ROH (40–49 kb) were found in abundance and equally distributed in all animals, whereas ROH longer than 59 kb showed a distinct distribution among different populations. Longer ROH (>400 kb) and high inbreeding coefficients in Sorraia and Thoroughbred horses were attributed to a closed population, and in Arabian horse, it was attributed to a limited genetic base (Aberle *et al.* 2004; Khanshour *et al.* 2013b). The low genetic diversity and high inbreeding in Thoroughbred horses may be a result of selective pressure on racing performance traits (Gu *et al.* 2009).

Beynon *et al.* (2015) inferred population history and structure of Welsh sheep breeds using the haplotype homozygosity (HHn) method. This method relies on the genome-wide distribution of ROH. The inference using HHn reflected a very large ancestral population size, which has been sharply reduced since then. This steep reduction could reflect the Last Glacial maximum, which occurred 20 000 to 30 000 years ago (Clark *et al.* 2009), and the domestication event that occurred 12 000 years ago (MacLeod *et al.* 2013).

An overview of the mean number of ROH per animal and the mean genome coverage in different livestock species is given in Table 2. Horses showed the highest proportion of the genome covered by ROH and the highest mean number of ROH per animal, followed by pigs, which also showed a high ROH genome coverage. Based on the data shown in Table 2, further research is called for in species such as horse, sheep and goat, because results so far are sparse and do not allow a direct comparison of ROH patterns. In addition, it is necessary to determine whether results reflect population phenomena or are biased (over- or under-estimation) due to the set of parameters used to perform ROH analysis.

ROH and molecular estimates of relatedness and inbreeding

The inbreeding coefficient has traditionally been estimated mainly from the information derived from pedigree data since Wright's (1922) work. The recent development of high-density SNP arrays led to an increasing interest in calculating the inbreeding coefficients from molecular information in livestock (Ferenčaković *et al.* 2011, 2013a; Purfield *et al.* 2012; Bjelland *et al.* 2013; Silió *et al.* 2013; Marras *et al.* 2014; Saura *et al.* 2015; Zavarez *et al.* 2015); molecular data are more effective for estimating autozygosity and for detecting the effects of inbreeding than are pedigree data (Keller *et al.* 2011). It is not uncommon for pedigree data to contain errors (Ron *et al.* 1996). Further, pedigree relatedness is estimated from statistical expectations of the probable proportion of genomic identity by descent, whereas genotype-based estimates show the actual relatedness among individuals (Visscher *et al.* 2006).

As a result, molecular information has introduced significant advances into the analyses of inbreeding coefficients, i.e. inbreeding estimated from observed homozygous genotypes and from ROH (F_{ROH}). Observed homozygosity can be defined as the proportion of homozygous loci at either the individual or population level (Allendorf 1986; Avise 1994), and it is an alternative measure of inbreeding (Li *et al.* 2011).

F_{ROH} estimates present several advantages compared to F_{PED}. F_{ROH} more accurately predicts the current autozygotic percentage of the genome and detects autozygosity due to common ancestry even 50 generations previously (Howrigan *et al.* 2011; Keller *et al.* 2011). It can be estimated in any genotyped animal, even when the pedigree information is not available, and also allows for the examination of genome autozygosity distribution to find the specific locations with high levels of autozygosity, for example, to estimate the F_{ROH} separately for different chromosomes (Keller *et al.* 2011). Besides, F_{PED} assumes that the entire genome does not undergo selection (Curik *et al.* 2002) and recombination events and, therefore, does not take into account potential bias from these events (Carothers *et al.* 2006). This variance increases with every meiosis (McQuillan *et al.* 2008) and relies on recombination events that occur during the formation of gametes (Bjelland *et al.* 2013).

The moderate to high correlations between F_{PED} and F_{ROH} illustrate that F_{ROH} estimates can be applied as an indicator of inbreeding levels in a number of cattle and swine breeds (Table 3). It is worth mentioning that F_{PED}–F_{ROH} correlation increases with ROH length. According to Marras *et al.* (2014), this may be explained by considering that ROH reflect both past and recent relatedness and that F_{PED} estimates are based on pedigree records, which may not extend back many generations. When longer ROH reflecting recent relatedness are considered to calculate F_{ROH}, the F_{PED}–F_{ROH} correlation tends to be higher. Saura *et al.* (2015) reported that the average $F_{ROH>5Mb}$ was very close to F_{PED}, whereas the average $F_{ROH<5Mb}$ was about four times lower than the average F_{PED}.

Scraggs *et al.* (2014) suggested that the F_{PED} underestimates the true relatedness of Wagyu cattle because differences in inbreeding coefficient levels between F_{PED} and F_{ROH} were observed. They reported lower estimated F_{PED} compared to F_{ROH}. These results are consistent with the data obtained for cattle (Marras *et al.* 2014; Kim *et al.* 2015a) and pigs (Saura *et al.* 2015), in which F_{ROH} gave a higher estimate, suggesting that F_{PED} may possibly be underestimating inbreeding. In horses, Metzger *et al.* (2015) estimated F_{ROH}, but did not correlate it to F_{PED}. F_{ROH} estimates for 50-SNP windows ranged from 0.18 to 0.43. Guangul (2014) estimated F_{ROH} in five goat populations at different run lengths (>1 to >16 Mb) and found values ranging from 0.0048 (F_{ROH} > 16 Mb) to 0.0500 (F_{ROH} > 1 Mb). A more recent study found F_{ROH} values ranging from 0.02 to 0.09 in goats and 0.02 to 0.10 in sheep (Kim *et al.* 2015b). An overview of F_{ROH} levels and mean F_{ROH} for different species, such as human, cattle and pig, is available in Curik *et al.* (2014).

According to previously described studies, we can conclude that F_{ROH} is a better tool for quantifying inbreeding. Our conclusion is based on limitations of F_{PED}. Pedigree-based inbreeding estimates fail to capture the actual proportion of the genome that is IBD; hence, animals in the founder population may be classified as unrelated. Also, the probabilistic approach of F_{PED} does not account for stochastic variations during meiosis. We believe that these shortcomings may be responsible for underestimated or erroneous F_{PED} estimates. The advantage of F_{ROH} goes further in identifying IBD segments with a greater accuracy. F_{ROH} estimates can disclose the age of the inbreeding based on the length of the ROH, which is an important tool in population genetics.

Deleterious variants and inbreeding depression through detected ROH

Charles Darwin (1876) reported that inbreeding could lead to reduced productivity in plants, and Garrod *et al.* (1996) realized that some traits in humans, such as albinism and alkaptonuria, occurred more frequently in progeny derived from consanguineous marriages. Garrod *et al.* (1996) studied the pattern of recessive inheritance proposed by Mendel (1866) and observed that the high incidence of recessive diseases in inbred individuals resulted from the high probability that they were homozygous for a deleterious recessive allele inherited IBD. The deleterious recessive variants can be identified in inbred individuals by the presence of long homozygous regions (Lander & Botstein 1987) or by studying the ROH (Broman & Weber 1999). Szpiech *et al.* (2013), and Zhang *et al.* (2015) observed a strong linear relationship between the frequency of deleterious homozygous variants and the genomic ROH fraction, with values of 0.98 and 0.93 respectively. Szpiech *et al.* (2013) reported that individuals with a high ROH coverage had a higher fraction of deleterious variants occurring in long ROH, which is in agreement with the hypothesis that recent inbreeding enables rare deleterious variants to exist in homozygous form. Additionally, Zhang *et al.* (2015) observed that deleterious homozygotes occur more frequently in ROH regions than do non-deleterious homozygotes. Therefore, the role played by autozygosity has contributed to an ongoing interest in determining whether these segments are correlated to risk factors for simple and complex diseases (Howrigan *et al.* 2011) and to inbreeding depression (Charlesworth & Willis 2009).

Biscarini *et al.* (2014a) studied the distribution of functional bovine variants and used ROH to detect genomic regions associated with susceptibility to infectious, metabolic and reproductive diseases, and the risk of mastitis and

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Table 3 Correlations between the inbreeding from pedigree data (F_{PED}) and from molecular information through runs of homozygosity (F_{ROH}) for different ROH length and livestock species.

					r						
Author	Species	SNP array	Breed/population	*n*	F_{PED}, F_{ROH}	F_{PED}, $F_{ROH>1Mb}$	F_{PED}, $F_{ROH>2Mb}$	F_{PED}, $F_{ROH>4Mb}$	F_{PED}, $F_{ROH>5Mb}$	F_{PED}, $F_{ROH>8Mb}$	F_{PED}, $F_{ROH>16Mb}$
Ferenčaković *et al.* (2011)	Cattle	Illumina Bovine SNP 50 K BeadChip	Austrian Simmental	500	–	0.64[1]	0.67[1]	0.68[1]	–	0.68[1]	0.63[1]
Purfield *et al.* (2012)	Cattle	Illumina BovineHD Genotyping BeadChip assay	Multiple breeds[2]	891[2]	0.71[3]	–	–	–	–	–	–
Ferenčaković *et al.* (2013a)	Cattle	Illumina Bovine SNP 50 K BeadChip	Brown Swiss	304	–	0.66[1]	0.67[1]	–	–	0.60[1]	0.50[1]
			Fleckvieh	502	–	0.66[1]	0.69[1]	–	–	0.70[1]	0.64[1]
			Nowegian Red	498	–	0.61[1]	0.61[1]	–	–	0.62[1]	0.53[1]
			Tyrol Grey	117	–	0.71[1]	0.72[1]	–	–	0.71[1]	0.70[1]
Kim *et al.* (2013)	Cattle	Illumina Bovine SNP 50 K BeadChip	Unselected line	299	0.62[4]/0.60[5]	–	–	–	–	–	–
			Contemporary Holsteins	1634	0.68[4]/0.64[5]	–	–	–	–	–	–
			Selected line for milk production	151	0.59[4]/0.58[5]	–	–	–	–	–	–
Marras *et al.* (2014)	Cattle	Illumina Bovine SNP 50 K BeadChip	Italian Holstein	2093	–	0.70		0.69	–	0.65	0.56
			Italian Brown	749	–	0.66		0.66	–	0.65	0.58
			Italian Simmental	479	–	0.66		0.74	–	0.76	0.71
Pryce *et al.* (2014)	Cattle	Illumina Bovine SNP 50 K BeadChip	Holstein	8853	0.53	–	–	–	–	–	–
			Jersey	4138							
Neves *et al.* (2015)	Cattle	Illumina Bovine SNP 50 K BeadChip	Gyr	25	–	–	0.39	0.40	–	0.40	–
Kim *et al.* (2015a,b)	Cattle	Illumina Bovine SNP 50 K BeadChip	Jersey	1062	0.70[6]/0.71[7]						
Zhang *et al.* (2014)	Swine	Porcine SNP60 Beadchip	Yorkshire	2358	0.69						
Silió *et al.* (2013)	Swine	Porcine SNP60 Beadchip	Iberian	64	–	0.77[8]				0.81[8]	
Saura *et al.* (2015)	Swine	Porcine SNP60 Beadchip	Guadyerbas	109	0.63	−0.24				0.60	

[1]Pedigree inbreeding coefficients referred to all generation long.
[2]Angus ($n = 39$), Hereford ($n = 40$), Belgian Blue ($n = 38$), Charolais ($n = 117$), Friesian ($n = 98$), Holstein ($n = 262$), Holstein-Friesian crosses ($n = 111$), Limousin ($n = 128$) and Simmental ($n = 58$).
[3]Value defined using the parameters set for the HD panel genotypes in which the sum of ROH per animal was set as ROH > 500 kb.
[4]Values defined using a 50 SNP sliding window.
[5]Values defined using a 100 SNP sliding window.
[6]Definition of ROH based on the number of continuous homozygous SNPs (100 SNPs).
[7]Definition of ROH based on the number of continuous homozygous SNPs (30, 50 and 80 SNPs).
[8]Values for genealogical inbreeding coefficients tracing the pedigree back to the founder animals (F26G) and tracing the pedigree back five generations to common ancestors (F5G).

locomotion disorders in dairy cattle. They were able to identify the prevalence of ROH in regions that contain important genes that trigger the diseases. One example is the ROH located at 12 Mb on BTA12, which contains the *VWA8* gene, whose mutations might be associated with musculoskeletal disorders and coagulation abnormalities. ROH associated with reproductive problems were found on BTA 5, BTA 15 and BTA 18. Susceptibility to infectious diseases was found on BTA 7 and BTA 12. Biscarini *et al.* (2013) also used ROH to study causal mutations for arthrogryposis and macroglossia in Piedmontese cattle.

Muchadeyi *et al.* (2015) examined Swakara sheep, looking for extended ROH shared across animals associated with sub-vitality performance. Consensus overlapping ROH (cROH) in sub-vital sheep were observed on chromosomes 3, 4 and 25. These cROH regions carried genes impacting the nervous system and skeletal and brain development, such as *LRRTM3*, *DPP6* and *SHH*. Despite the findings, they were unable to support the presence of a recent recessive-lethal mutation causing the sub-vital phenotype.

Scanning the genome for ROH might be an alternative or complementary strategy to genome-wide association studies (GWAS) for complex disease traits (Biscarini *et al.* 2014b). Huson *et al.* (2014) utilized genome-wide association, haplotype analysis, signatures of selection and ROH analysis to identify a consensus region for the SLICK locus on BTA20 in cattle. Mészáros *et al.* (2015) utilized ROH and GWAS analysis to identify genomic regions of entropion in Austrian Fleckvieh cattle. Biscarini *et al.* (2015b) studied different methods to identify QTL in farm animals instead of traditional GWAS, namely resampled predictive models (Biffani *et al.* 2015) and a ROH-based approach. Kim *et al.* (2015a) used genome-wide association testing to explore potential negative correlations between the occurrence of ROH and daughter pregnancy rate and/or somatic cell score in US Jersey cattle.

The genetic basis of inbreeding depression is caused by an increased rate of homozygosity (Charlesworth & Willis 2009) and frequency of homozygous deleterious alleles (Ouborg *et al.* 2010; Ku *et al.* 2011), which leads to reduced individual performance and decreased population variability (Gonzalez-Recio *et al.* 2007). The performance reduction in plant and animal populations due to inbreeding depression has been described by Charlesworth & Willis (2009). The reduced performance and diversity in populations lead to a reduced selection response of breeding programs (Weigel 2006). Thus, the study of inbreeding depression and its negative consequences are considered indispensable for conservation genetics studies and for breeding program management (Keller & Waller 2002).

Pryce *et al.* (2014) estimated inbreeding depression for milk production and fitness traits using pedigree-based inbreeding coefficients. Increased F_{PED} and F_{GRM} (diagonal of the genomic relationship matrix minus 1) by 1% in Holstein cows was associated with a decrease in milk yield of 21 and 28 liters/lactation respectively. For Jersey cows, this reduction was 12 and 27 liters/lactation respectively. The association of F_{PED} with fertility was significant ($P < 0.005$) only for Holstein cows, for which a 1% increase was associated with a calving interval extension of +0.18 days. Also, decreases in milk, fat and protein yields in Holstein and Jersey cows was associated with a 1% increase in homozygous SNPs. Kim *et al.* (2015a) recognized that more than 60 regions displayed increased ROH levels, which can be correlated to a F_{PED} increase in US Jersey cattle in the last five decades. A negative association between the occurrence of ROH and daughter pregnancy rate was observed on BTA 3, BTA 7, BTA 8 and BTA 12. The same pattern was observed for somatic cell score. An increase of ROH levels based on F_{PED} influenced somatic cell score on BTA 1, BTA 3, BTA 4, BTA 5, BTA 13 and BTA 21, suggesting that high autozygosity due to inbreeding may potentially influence fertility and be related to susceptibility to mastitis.

A study to test inbreeding depression on post-weaning growth performance in pigs was performed by Silió *et al.* (2013). Their estimates of inbreeding depression were expressed by the decreasing performance relative to the mean per a 0.10 increase in inbreeding coefficient, which were –4.40% for daily gain and –1.52% for weight at 90 days. Saura *et al.* (2015) observed genomic regions responsible for inbreeding depression for two reproductive traits in a highly inbred line of Iberian pigs (Guadyerbas pigs). A reduction in number of piglets born alive and in the total number of piglets born was also observed per a 10% increase in inbreeding.

These findings suggest that inbreeding increases autozygosity throughout the genome and may trigger the expression of homozygous recessive alleles that may cause expression of an unfavorable phenotype (Agerholm *et al.* 2001). Understanding when deleterious mutations arose and why they persist in populations is of interest in breeding and conservation programs (Schubert *et al.* 2014; Marsden *et al.* 2016). Marsden *et al.* (2016) demonstrated that, rather than just avoiding inbreeding, a large population size is critical for preventing the accumulation of deleterious variants. Thus, we believe that further efforts need to be made in conservation genetics programs to avoid environmental population segregation. If this is not accomplished in time, the accumulation of deleterious variants and the occurrence of genetic erosion will lead to more severe consequences than the ones triggered by the inbreeding itself.

Effect of artificial selection on ROH

The identification of recent selection signatures in the genome provides relevant information regarding the response to strong directional selection in domesticated animals. The selection of superior animals reduced

phenotypic variability and reshaped the genome, including ROH patterns, when compared to not intensively selected animal groups (Kim *et al.* 2013). The search for superior animals via selection has reduced the diversity of haplotypes and has increased homozygosity around the target locus, generating high frequency of ROH in regions that house the selection targets (Leocard 2009; Karimi 2013; Zhang *et al.* 2015).

Zhang *et al.* (2015) observed that ROH patterns were not randomly distributed across the genome. A number of ROH peaks were distributed and shared among individuals, which is likely the result of selection events and not attributable only to demographic history. Genomic regions that are selection targets tend to generate ROH islands, defined as genomic regions with reduced genetic diversity and, consequently, high homozygosity around the selected locus compared to the rest of the genome (Pemberton *et al.* 2012). According to Sonesson *et al.* (2010), there is a risk that the genomic selection can also result in long homozygous segments around QTL regions in populations that were selected for any given trait.

Purfield *et al.* (2012) observed that the genomic regions located on BTA 7, BTA 14, BTA 16 and BTA 18, which had a high incidence of ROH, also contained important cattle genes associated with traits related to immunity, carcass and dystocia in calving. In particular, BTA 5 and BTA 9 had an increased number of long ROH (>20 Mb) and tended to contain QTL associated with milk fat production and growth traits in cattle. Kim *et al.* (2013) found that the longest ROH was 87.13 Mb on BTA 8 in a Holstein cow selected from an elite herd. The average number of ROH per individual in the control group, i.e. animals without selection, was significantly lower ($P < 0.0001$) compared to the animals that had undergone genetic selection. Animals belonging to groups with higher selection intensity had a high level of autozygosity in their genomes, especially in 13 regions of 11 chromosomes. Differences in patterns of ROH among populations support the possibility that animal selection affects the patterns of autozygosity in their genome. According to Pemberton *et al.* (2012), recent strong directional selection is expected to have a greater influence on long ROH compared to medium and small ROH because it tends to generate long haplotype segments.

Karimi (2013) studied some European (Angus, Fleckvieh and Brown Swiss) and zebu (Nellore, Gir and Brahman) cattle breeds and found six common regions in the genome of the two groups of animals located at regions associated with QTL for production on BTA 6 (38 268 200–39 451 000), BTA 7 (51 502 500–52 353 000), BTA 10 (24 575 700–25 619 800), BTA 12 (28 434 000–29 628 100), BTA 16 (43 802 200–44 968 700) and BTA 21 (1 360 390–1 853 150). These results suggest that natural and artificial selection may strongly shape genomic ROH patterns in livestock (Pemberton *et al.* 2012).

Khanshour (2013a) screened for candidate segments for positive selection performing ROH analysis in distinct Arabian horse populations. Metzger *et al.* (2015) studied the functional distribution of ROH in selected and non-selected horses and noticed that genes affecting cellular, metabolic and developmental processes, as well as the immune system and reproduction, were observed in ROH regions. The Hanoverian breed, which has been intensively selected for optimal performance, shared 18 ROH regions that harbored six relevant genes for morphology and performance in sport horses.

Intense selection and decreasing the effective population size through the selection of superior animals can endanger the viability and variability of populations in the long term (Saccheri *et al.* 1996). Selection tends to increase inbreeding rates, resulting in fixed alleles that cause major phenotypic changes and lead to loss of allelic variation (Muir *et al.* 2008). The studies reviewed above demonstrate the importance of managing the breeding programs to maintain heterozygosity in the chromosomal regions that house important genes for animal husbandry, thus keeping the genetic diversity around the selection target locus and avoiding the expression of deleterious variants throughout the genome.

Genetic diversity and ROH

In the last decade, there has been a sharp increase in the intensity of selection in breeding programs, especially in dairy cattle, pigs and poultry. The increased use of elite animals has contributed to increased inbreeding rates, reducing the effective population size. The low effective population size increases the effect of inbreeding and genetic drift and reduces the genetic variability, which may compromise the viability of populations and change the patterns of ROH in the long term (Frankham & Ralls 1998). These events are more accentuated in many local breeds with a small population size, predisposing them to extinction (FAO, 2013).

Genomic tools have been widely used to study and characterize the genetic diversity and population structure of livestock (Rothschild & Plastow 2014). Therefore, without pedigree data, in many breeds genetic markers can be used to estimate the effective population size, by for example, exploring the extent of LD (De Roos *et al.* 2008; Corbin *et al.* 2010; Uimari & Tapio 2011; Herrero-Medrano *et al.* 2013; Beynon *et al.* 2015). The estimated effective population size based on the recombination rate and LD provides useful predictions and consistent comparisons among populations (De Roos *et al.* 2008; Herrero-Medrano *et al.* 2013). The individual evaluation of ROH patterns also has practical implications for conservation programs. Animals with high levels of ROH may be excluded or used less frequently in mating populations threatened with extinction or with a small effective population (Herrero-Medrano *et al.* 2013; Biscarini *et al.* 2015a).

The mating or cross between outbred individuals or populations is an option for increasing genetic diversity, contributing to the disruption of long ROH in the genome. The effects of hybridization or outbreeding were observed in three African hybrid cattle breeds (Kuri, Sheko and Borgou) that had the shortest ROH among the studied African breeds (Purfield *et al.* 2012). In pigs, recent mating between domesticated Manchado de Jabugo animals and other breeds may have resulted in the breakdown of homozygous haplotypes longer than 100 Mb. The Manchado de Jabugo population showed no signs of high inbreeding, probably due to its mixed heritage, despite being highly endangered due to its small population size (Herrero-Medrano *et al.* 2013). Ai *et al.* (2013) observed that Chinese Kele pigs had the shortest ROH, leading to a hypothesis that this population has a historical admixture with Western pigs. This hypothesis was based on structural analysis, in which Kele pigs showed close phylogenic relationships and signals of admixture with Western pigs. The White Duroc breed showed the lowest fraction of autozygous segments in Western pigs. This may be attributed to the recent admixture of Duroc and Large White in the population, reducing the length of homozygous segment in the White Duroc genome. The same pattern, in which the pure sheep breeds had more ROH across the whole genome than did the crosses, was observed by Al-Mamun *et al.* (2015).

Maintaining genetic diversity within and across breeds is crucial in conservation genetics (Ollivier & Foulley 2005) to sustain livestock production. In this regard, studies using genomic measures of co-ancestry to minimize the loss of genetic diversity and inbreeding in conservation programs have been proposed (De Cara *et al.* 2013; Bosse *et al.* 2015; Gómez-Romano *et al.* 2016). A measure of co-ancestry based on IBD segments has been suggested as a strategy to maintain genetic diversity and fitness in conservation programs when the given population has a medium to high inbreeding load (De Cara *et al.* 2013). As discussed in this review, selection, low effective population size and inbreeding can negatively affect genetic diversity, and breeding programs must monitor genetic variation to prevent an irreversible erosion of genetic diversity in livestock populations, maximizing their capability to adapt to changes (Biscarini *et al.* 2015a).

Final considerations

The objective of this study was to give a comprehensive review of current knowledge and application of ROH in livestock and also to identify research gaps for future research areas. Studies involving homozygous segments have shown that ROH are common in the genome of livestock species and have addressed population history and their structure, selection pressure, inbreeding and the occurrence of deleterious variants throughout the genome. However, most of the studies involved dairy cattle and pig, and fewer were on beef cattle and other livestock species. Studies on a wider range of species are needed to better understand the genetic architecture and the effects of ROH in livestock.

Probably the major difficulty faced by scientists is the lack of consistent criteria among studies regarding the threshold values in each parameter analyzed to define a ROH. A number of software programs have been developed to infer ROH by applying different algorithms and methodologies, but there have been relatively few studies assessing which set of parameters is optimal for detecting ROH so as to better understand their effects on detecting autozygosity (Howrigan *et al.* 2011; Ferenčaković *et al.* 2013b; Karimi 2013; Mastrangelo *et al.* 2016). Even though some incipient standards can be seen among the studies, such as the number of heterozygous calls allowed being no more than two, further efforts need to be made to reduce biased values when defining a ROH. In addition, as stated in this review, the frequency and distribution of ROH in livestock is influenced by many factors, of which we highlight the populations' demographic history. However, to date, there have been no studies on the influence of the particularities of a specific population on the ability of these algorithms to infer ROH and to establish consistent criteria.

It has been well demonstrated that ROH is a more effective and accurate alternative for quantifying animal relatedness and inbreeding levels. Most of the ROH analyses have been heavily used for conservation purposes, to manage inbreeding, and in small and isolated populations to make them reservoirs of genetic variation. However, further research is necessary to quantify the impact of animal relatedness measures based on ROH on estimated breeding value (EBV) prediction and genetic evaluation reliability. In this regard, Luan *et al.* (2014) showed that predicting genomic EBV based on ROH showed higher or similar accuracy of genomic EBV prediction for simulated data in Brown Swiss cattle as compared to linkage analysis relationships. It is important to stress that, different from dairy cattle populations, in beef cattle and sheep populations the absence of pedigree information or the presence of incomplete pedigree with missing parents is more common. According to Berry *et al.* (2016), the development of accurate genomic evaluations in beef populations is more difficult than in dairy populations due to the existence of multiple breeds, poor extent of phenotyping, lack of artificial insemination, and beef systems being generally a lower-margin business and a poorer adopter of technology. Thus, for beef and sheep populations, it is expected that gains in EBV reliability from pedigree information based on ROH are likely to be somewhat higher than those in dairy cattle.

In recent years, the emergence of various next-generation sequencing platforms has enabled the sequencing of the full genome at lower cost and in shorter time. Next-generation sequencing platforms bring higher map resolution not only for ROH detection (Pippucci *et al.* 2014) but

also for other structural variations, such as genome copy number variation (Pirooznia *et al.* 2015). Despite the advances in high-throughput technologies and whole-genome sequencing analysis, tools to integrate the genomic structural variations with whole transcriptome analysis are necessary to better elucidate the genetic mechanisms that determine the genetic and phenotypic differences among animals, causal variation and loss of alleles. These technologies can assist in better understanding the autozygosity at work in livestock.

Conflict of interest

The authors declare that they have no conflict of interest.

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