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Comparison of diversity parameters from SNP, microsatellites and pedigree records in the Lidia cattle breed

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ABSTRACT

Genetic drift, loss of heterozygosity and decrease in genetic variability are consequences of high rates of inbreeding over generations.. High density single nucleotide polymorphisms arrays offered new possibilities to estimate inbreeding coefficients more accurately than those from pedigree records or microsatellites genotypes. In the present study different inbreeding coefficients were estimated and compared from SNP data: (1) runs of homozygosity of different length (>1Mb, > 4Mb, > 8Mb and > 16Mb), (2) inbreeding coefficients based on the observed vs. expected number of homozygous genotypes and (3) standardized observed homozygosity, from pedigree records and from three microsatellite derived diverse metrics. SNP inbreeding coefficients ranging from 0.14 to 0.26 and shown correlations ≥ 0.84 among them. The correlation among SNP and pedigree inbreeding coefficients was moderate ranged from 0.37 to 0.5 and low than the expected correlation. The limited pedigree depth of the Lidia cattle breed as revealed the average number of equivalent complete generations (5.5) probably explain that the higher correlation coefficient with pedigree records was with the runs of homozygosity of high length (>16Mb). Also, the absence of identity disequilibrium on our molecular data could explain the moderate correlation values (0.43–0.54 in absolute values) among microsatellite derived metrics and SNP inbreeding coefficients.

1. Introduction

The management of inbreeding has been a major concern in livestock populations. Inbreeding coefficient (F) is defined as the probability that, in a locus sampled randomly in a population, a pair of alleles are identical by descent (IBD) with respect to a base population where all alleles are independent (Wright, 1922). Loss genetic diversity, increase the frequency of recessive alleles and decrease performance traits of interest in animal science are the major consequences of mating related individuals in domesticated animal populations (Gonzalez-Recio et al., 2007; Bjelland et al., 2013). Traditionally, genealogical records have been used to estimate the inbreeding coefficients in cattle populations as demonstrated by Wright (1922). However, the estimation of quantitative genetic parameters is limited to the accuracy and completeness of the available pedigree information (Wang, 2016). The development of microsatellite markers provided new opportunities to refine the understanding of genetic variation in livestock populations (Defaveri et al., 2013; Fernández et al., 2005). The estimation of inbreeding coefficients from microsatellite markers are faster, cheaper and does not require breeding records over a number of generations. While microsatellite markers have been the method of choice to analyse genetic relationships among populations, especially when they are unrelated, the estimation of inbreeding coefficients from microsatellite markers explain only a tiny fraction of the variance of pedigree based values due to the high locus by locus variation of Mendelian segregation (Wang, 2016). Also, the comparison among pedigree and microsatellite inbreeding coefficients considered two types of different homozygosities (identity by state and identity by descent) (Hill and Weir, 2011; Vicente et al., 2012). Furthermore, the discussion of the number of microsatellite markers needed to accuracy inbreeding coefficient estimations is an old issue that date to the early 1980s (Mitton and Pierce, 1980; Chakraborty, 1981). The recent development of high density genotyping platforms offered new possibilities to increase the accuracy of estimated genetic diversity parameters in livestock populations. Inbreeding levels estimated from SNP data have been estimated using variance of genotype values (Van Raden, 2008) or their combination with levels of homozygosity (Yang et al., 2010). The analysis of Runs of Homozygosity (ROH), defined as continuous and uninterrupted stretches of DNA sequences without heterozygosity in diploid state (Gibson et al., 2006), have been proposed as an effective way for identifying IBD segments and to estimate inbreeding coefficients (Gibson et al., 2006; Lencz et al., 2007). Individual autozygosity is the

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consequence of individuals with common ancestors that pass shared chromosomal segments to their progeny and results in homozygous segments in their offspring that increase the number of ROH (Broman and Weber, 1999). The length of the ROH is proportional to the nearest of common ancestors because recombination events interrupt long chromosome segments. So long ROH are expected to be originated from recent common ancestors while short ROH from more remote ancestors. Recently, Peripolli et al. (2017) review the current knowledge and applications in livestock of ROH and revealed their ability for the understanding of the demographic evolution of populations. Several advantages have been argued when individual inbreeding coefficients are estimated from ROH (F_{ROH}) as the higher precision to achieve the current autozygotic percentage of the genome or the detection of autozigosity due to common ancestors even 50 generations ago. So, ROH have been postulated as the better option for quantifying inbreeding (Peripolli et. al, 2017). However, differences in the methodology applied to identify ROH could vary considerable the results and should be considered with caution.

In spite of several studies have been compared pedigree-genomic SNPs or pedigree-microsatellites inbreeding estimations (Silio et al., 2013; Zhang et al., 2015; Wang, 2016), comparisons among them (pedigree, microsatellites and SNPs) are scarce.

In the present study the three main sources of information (pedigree, microsatellites and SNPs) traditionally used to estimate inbreeding coefficients and/or genetic diversity parameters have been compared in the Lidia cattle breed, in which the genetic biodiversity have been widely analyzed with pedigree records, paternal and maternal DNA markers, autosomal microsatellites and recently with SNPs (Cañon et al., 2008; Cortes et al., 2008, 2011, 2014; Eusebi et al., 2017).

2. Material and methods

Pedigree records, microsatellite and Bovine SNP 50k (Illumina, 2011) genotypes were available for a total of 284 Lidia breed animals. All the animals analyzed belonging to lineages recognized as conforming to the official breed standard (RD 60/2001, Boletín Oficial del Estado, 2001).

2.1. Genealogical data

Genealogical records were provided for the Union de Criadores de Toros de Lidia (U.C.T.L.). Previous genealogical analysis achieved index of completeness over the last ten generations and equivalent complete generations of 99% and 6.3% respectively in those animals born after 2004 (Cortés et al., 2014). The equivalent number of complete generations, number of maximum generations and coefficients of inbreeding based on genealogical information (F_P) were calculated using the PEDIG software (Boichard, 2002).

2.2. Microsatellites

The 24 microsatellite loci studied, chromosomal locations and laboratory protocols are described in details in Canon et al. (2008). A total of 4 heterozigosity measures were calculated with the software GENHET (Coulon, 2010).

PHt: Proportion of heterozygous loci in an individual (number of heterozygous loci / number of genotyped loci). $sMSLH_o$: standardized heterozygosity based on the mean observed heterozygosity (PHt / mean observed heterozygosity of typed loci).

IR: Internal relatedness (IR) (Amos et al., 2001)

$$IR = \frac{2H - \sum f_i}{2N - \sum f_i}$$

where H is the number of loci that are homozygous, N is the number of loci and f_i is the frequency of the i_{th} allele contained in the genotype.

HL: Homozygosity by locus (Aparicio et al., 2006):

$$HL = \frac{\sum E_h}{\sum E_h + \sum E_j}$$

where $E_h$and E_j are the expected heterozygosities of the loci that an individual bears in homozygosis (h) and in heterozygosis (j), respectively.

2.3. SNP

Bovine SNP 50k genotypes were filtered with PLINK 1.9 (Purcell et al., 2007) software excluding SNPs mapping to sexual chromosomes, individuals with less than 10% of missing genotypes and those that failed the frequency test setting a minimum allele frequency threshold of 0.01. A total of 42,458 SNP were retained after quality controls and used to estimated standardized observed homozygosity ($sSNP_{Ho}$) and inbreeding coefficient (F_{plink}) (based on the observed vs. expected number of homozygous genotypes) with the – het command. The standardized observed homzygosity ($sSNP_{Ho}$) was calculated as SNP_Ho/ mean observed homozygosity. Furthermore, four additional inbreeding coefficients based on ROH were calculated. Previously, data were pruned considering that high linkage disequilibrium (LD) can lead to detection of ROH that are not truly IBD. LD pruning was also performed before the ROH call to increase power, as suggested by Purcell et al. (2007), with the –indep PLINK command, and the following parameters: a window size in SNPs of 50, the number of SNPs to shift the window at each step of 5 and a r^2 threshold of 0.5. The number of SNPs after pruning was 31,243. To minimize the number of false positives, the minimum number of SNPs that constituted a ROH (l) was calculated by a method similar to that proposed by Lencz et al. (2007):

$$l = \frac{log_e \frac{\alpha}{n_s n_i}}{log_e(1 - het)}$$

where n_s was the number of genotyped SNPs per individual, n_i was the number of individuals, α was the percentage of false positive ROH (set to 0.05 in the present study) and *het* was the mean SNP heterozygosity across all SNPs. ROH were detected using the following settings: the minimum number of SNP needed to define a ROH was 69 (as defined the equation explained above), 0 number of missing class allow, a minimum density of one SNP every 100 kb, a maximum gap length of 1000 kb, no missing genotypes and 1 heterozygous SNP loci, and number of heterozygous call allowed 1. Finally, the inbreeding coefficient based on ROH (F_{ROH}) was defined as the length of the genome present in ROH, divided by the overall length of the genome covered by SNPs (Leutenegger et al., 2003). This overall was taken to be 2,500,625 (Purfield et al., 2012). For each sample, we calculated genomic inbreeding coefficients ($F_{ROH>1Mb}$, $F_{ROH>2Mb}$, $F_{ROH>8Mb}$ and $F_{ROH>16Mb}$) derived from ROHs with different lengths (> 1, > 2, > 8 or > 16 Mb).

A strong correlation between microsatellite and SNPs heterozygosity estimates is only expected under substantial Identity Disequilibrium (non-random association of diploid genotypes between loci) (Fischer et al., 2017). To measure Identity Disequilibrium (ID) the program InbreedR (Stoffel et al., 2016) was used to calculate the g^2 statistic. Assessment of significant levels of ID ($g^2 > 0$) utilized 1000 resampling iterations.

The data were not normally distributed (Saphiro–Wilkins test), so Spearman correlations were calculated between the different genetic diversity parameters values of each molecular marker (microsatellite and SNP), and between them and the genealogical inbreeding coefficient. Also, the predicted correlation value between pedigree inbreeding coefficient and SNP and microsatellite individual heterozygosity was calculated following the expression proposed by Slate et al. (2004):

Table 1
Average and standard deviation of inbreeding coefficients inferred from pedigree records (F_P) and SNP, and diversity derived metrics estimated from microsatellite genotypes. Standard deviations in brackets. IR: Internal Relatedeness; HL: Homozygosity by Locus; sMLSHo: standardized Multilocus Heterozygosity; sSNPHo: standardized Observed Homozygosity with SNPs.

Pedigree		Microsatellites		SNP	
F_P	0.13 (0.09)	sMLSHo	1 (0.25)	F_{PLINK}	0.26 (0.10)
		IR	0.34 (0.17)	F_{sSNPHo}	0.14 (0.08)
		HL	0.51 (0.13)	$F_{ROH>1Mb}$	0.22 (0.09)
				$F_{ROH>4Mb}$	0.24 (0.09)
				$F_{ROH>8Mb}$	0.21 (0.09)
				$F_{ROH>16Mb}$	0.21 (0.09)

$$r(H, f) = \frac{\sigma(f)}{(1 - E(f))\sigma(f)}$$

where $\sigma(f)$ is the standard deviation of f and $E(f)$ is the mean of f.

3. Results

3.1. Microsatellites

Individual heterozygosity values based on microsatellite markers, was traditionally used as surrogates of inbreeding coefficients. The mean value of the standardized observed heterozygosity ($sMLH_o$) was 1, ranging from 0.07 to 1.7. The standardization seeks to ensure that multilocus heterozygosity (MLH) of all individuals is measured in the same scale in spite of the differences in marker information. The differences among IR (0.34) and HL (0.51) average values could be explained because IR is based on allele frequencies while HL take into account that some loci are more informative than others as weighs the contribution of loci depending on their allelic variability, so a locus will have more weight as increase the number of alleles of the locus and their frequencies are more balanced (Table 1). Aparicio et al. (2006) concluded that IR may be more efficient in populations with high inbreeding, as the Lidia breed, and HL in those with migration or admixture.

3.2. Single nucleotide polymorphism

A total of five of the six inbreeding coefficients estimated from SNP data shown similar average values (≈0.21–0.26) while F_{sSNPHo} evidenced the lowest one (0.14) (Table 1). The observed homozygosity with SNP markers was higher than that with microsatellite markers (0.75 and 0.52 respectively) and achieved low levels of genetic diversity in the Lidia cattle breed as previously reported Cañon et al. (2008) with autosomal microsatellite markers. It is remarkable the apparent absence of ID in our molecular data as all g^2 estimates were non-different from zero ($p < 0.05$).

3.3. Pedigrees

The average F_P was 0.13 and ranged from 0 (in 5 animals) to 0.5 (in 3 animals) (Table 1). The average number of equivalent complete generations and the number of maximum generation was 5.5 and 7.9 respectively for the 284 Lidia breed animals analyzed. It is well documented the high inbreeding values in the Lidia cattle breed consequence of the reduced effective number within the reproductive units which are called “encastes” and the reproductive isolation among them (Cortes, et al., 2014).

3.4. Correlation coefficients

The correlation coefficients between genetic parameters within molecular marker types (microsatellites and SNPs) shown high values, being higher within microsatellites (≥0.99) than within SNPs (≥0.82) (Table 2 and Fig. 1). However, the correlation among microsatellite and SNP inbreeding coefficients were moderate, ranging from −0.40 to −0.54. Also, similar moderate correlation coefficients were achieved among SNP inbreeding coefficients and HR and IL (≥0.41 and 0.55 ≤).

The correlations among the microsatellite genetic parameters with F_P were weak and of similar magnitude (−0.25 or 0.25), and in agreement with previous studies which compare both sources of information (Slate et al., 2004; Fernández et al., 2005) (Table 2 and Fig. 1). Also, the expected correlations among sMLH and F_P (0.38) was higher than the observed correlation (0.25). While F_P takes into account IBD, microsatellite markers refers to identity by state, and this difference partly explain the weak correlation among both sources of information, especially when the number of markers is low or the pedigree information is not deep enough. Furthermore, all microsatellite parameters were greater than F_P (Table 1). This could be explained by the relationships between genealogical and molecular metrics (Alves et al., 2008).

In spite of a SNP marker are less informative than an average microsatellite, the large number of SNPs that could be analyzed offset this disadvantage (Santure et al., 2010). It is remarkable the higher expected correlation among SNP heterozygosis and inbreeding coefficient from pedigree records (−0.9). However, the observed correlations among the genetic parameters estimated using SNPs and F_P shown low to moderate values (0.37–0.5) (Table 2 and Fig. 1). The correlation F_P-$F_{ROH>16Mb}$ was the higher correlation (0.5), while the correlation F_P -$F_{ROH>1Mb}$ was the lowest (0.37). Moderate to high correlations between F_P and F_{ROH} have been previously achieved in cattle breeds, being the majority of them higher than 0.6 (Peripolli, et al., 2017) and also higher than our results.

Table 2
Spearman correlation coefficients among inbreeding coefficients estimated from the pedigree and SNP, and diversity derived metrics estimated from microsatellite genotypes. ($p < 0.05$). IR: Internal Relatedeness; HL: Homozygosity by locus; sMLSHo: standardized multilocus heterozygosity; sSNPHo: standardized observed homozygosity.

		SNP						Microsatellites		
		$F_{ROH>1Mb}$	$F_{ROH>4Mb}$	$F_{ROH>8Mb}$	$F_{ROH>16Mb}$	F_{sSNPHo}	F_{PLINK}	F_{sMLSHo}	IR	HL
SNP	$F_{ROH>1Mb}$									
	$F_{ROH>4Mb}$	0.95								
	$F_{ROH>8Mb}$	0.91	0.99							
	$F_{ROH>16Mb}$	0.82	0.92	0.95						
	F_{sSNPHo}	0.84	0.92	0.93	0.89					
	F_{PLINK}	0.84	0.92	0.93	0.89	1.00				
Micorsatellites	sMLSHo	−0.43	−0.46	−0.45	−0.40	−0.54	−0.53			
	IR	0.45	0.48	0.46	0.42	0.55	0.54	−0.99		
	HL	0.45	0.47	0.46	0.41	0.54	0.54	−0.99	0.99	
Pedigree	F_P	0.37	0.41	0.45	0.50	0.44	0.44	−0.25	0.25	0.25

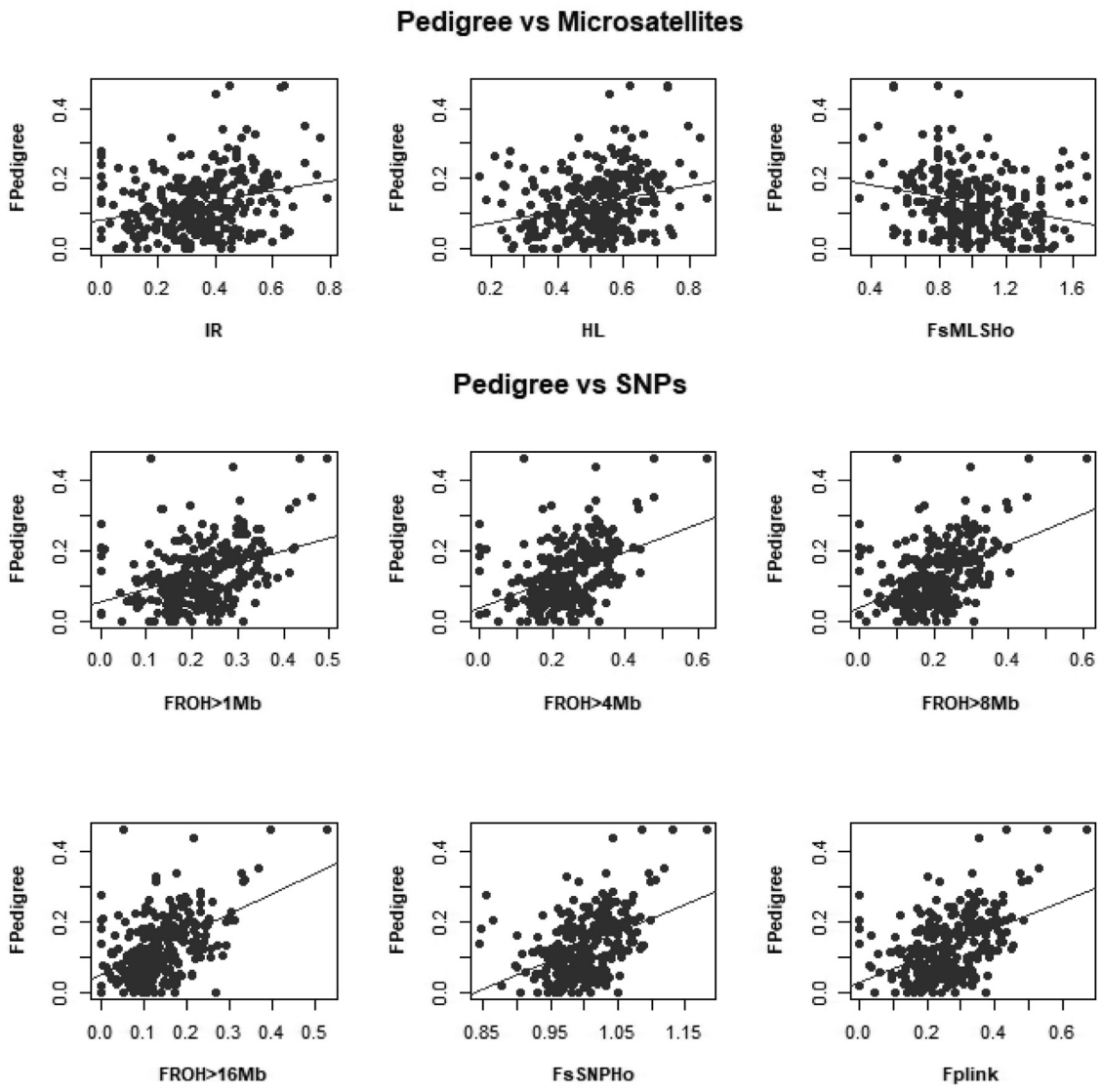

Fig. 1. Scatterplots of inbreeding pedigree coefficients versus SNPs ($F_{ROH>}$1 MB, $F_{ROH>}$4 MB, $F_{ROH>}$8 MB, $F_{ROH>}$16 MB, F_{sSNPHo}, F_{PLINK}) and microsatellite (IR, HL, F_{sMLSHo}) derived diversity parameters. IR: Internal Relatedeness; HL: Homozygosity by locus; sMLSHo: standardized multilocus heterozygosity; sSNPHo: standardized observed homozygosity.

4. Discussion

Pedigrees have long been preferred to measure individual inbreeding (Howard et al., 2017). However in absence of genealogical records, molecular markers have been widely used to measure inbreeding in wild and livestock populations Wang (2016). Many previous studies have reported weak correlations among pedigree inbreeding coefficients and microsatellite derived metrics of inbreeding (Slate et al., 2004; Fernández et al., 2005). The expected correlation between both sources of information is intuitively explained because higher homozygosity throughout the genome in inbred animals is also expected. However, both values do not measure the same phenomenom. While inbreeding coefficients are defined as the probability that the two homologous alleles in a population are identical by descent, microsatellite inbreeding coefficients are based on homozygous genotypes that could be IBD (autozygous) or identity by state (allozygous). Furthermore, the traditionally low number of microsatellites used and inaccurate or incomplete pedigree records could also explain the low correlation of both sources of information. Slate et al. (2004) analyzed the relationships between pedigree inbreeding coefficients (F_{PED}) and the heterozygosities based on microsatellite markers (SHM), and revealed a mean value of the expected and observed correlation r (SHM,F_{PED}) of -0.27 and -0.26 respectively and assessed that the relationship was largely insensitive to mean (f) and very dependent of σ^2(f). In spite of the higher $\sigma^2(F_P)$ values in the Lidia cattle breed (0.007) than that in previous publications with wild and domestic animal populations (0.005) (Slate et al., 2004), the expected correlation r (sMLH,F_P) was low (-0.38) and clearly higher than the observed (-0.25) which suggests that heterozygosity is a poor indicator of F. Also, the correlation among SNPs and microsatellite derived metrics were low, ranging from 0.41 to 0.54. Previous studies indicated that strong correlations is only expected when the studied populations are characterized by substantial ID, i.e. non-random associations of diploid genotypes between loci (Grueber et al., 2011). It is suggested that both drift within subpopulations and gene flow among subpopulations shape the distribution of ID. Previously it was achieved high levels of genetic differentiation among Lidia breeders as a consequence of the high reproductive isolation among them (Cañon et al., 2008). It is remarkably that the average F_{ST} genetic distance among Lidia breed lineages (0.18) is much higher than values among European cattle breeds ranged from

0.07 to 0.10. So, the absence of gene flow among Lidia breeders could explain the absence of ID in our data and as a consequence the weak correlation observed among molecular markers derived metrics and pedigree inbreeding coefficients.

In recent years with the availability of high-density SNP markers in livestock populations several authors have used runs of homozygosity (ROH) to estimate inbreeding coefficients (Peripolli et al., 2017). The setting of the parameters to define a ROH is crucial and could vary considerable their number and distribution through the genome. Recently, Rodriguez-Ramilo and Fernandez (2016) concluded that the maximum number of missing genotypes and the maximum number of heterozygous have no effect in the identification of ROH, while minimum length, minimum number of SNPs, minimum SNP density and maximum distance between two adjacent SNPs have a great influence and therefore in the estimation of F_{ROH}. Lencz et al. (2007) proposed a formula to estimate the minimum number of SNPs needed to define a ROH according to the availability SNP density. Furthermore, to avoid false ROH due to LD Purcell et al. (2007) developed a methodology to prune a subset of markers that are in linkage equilibrium with each other. Once implemented the methodologies described above the total number of SNPs analyzed was 32,261 and we defined ROH tracts as 69 continuous homozygous SNPs, a minimum density of one SNP every 100 kb, a maximum gap length of 1000 kb, no missing genotypes and 1 heterozygous SNP loci. Our results evidenced similar average F_{ROH} in the length class of 1, 4 and 8 Mb while the average $F_{ROH} > 16$ Mb was clearly lower (0.14). ROH length is related with the time elapsed from the generation of the inbreeding, e.g. ROH > 1, > 8, > 16 Mb represent up to 50, 6 and 3 generations from common ancestors respectively, so the correlation among F_P and F_{ROH} is dependent of the pedigree depth (Ferencakovic et al., 2013a). In the Lidia breed the average number of complete equivalent generations was 5.5, so F_P estimates are based in few back generations pedigree records. As a consequence, when long ROHs, which arise from recent inbreeding events, are considered, the correlation among F_P and F_{ROH} increase. A similar result in inbreeding correlations based in genome and pedigree data were achieved in human and cattle populations (McQuillan et al., 2008; VanRaden et al., 2011; Ferencakovic et al., 2013a, b). However the highest correlation achieved among metrics derived from SNP and F_P (0.5) was clearly lower than the expected correlation (0.9) derived from Slate et al. (2004). The same author achieved expected correlations (r (sMLH,F_{PED})) ranging from −0.08 to −0.71, that are highly sensitive to σ^2(f) magnitude, and observed correlations ranging from −0.04 to −0.72 in wild, captive and domestic populations. In spite of the difficulty to compare different studies due to the differences in the definition of a ROH, our correlations estimations among SNP and F_P are lower than that reviewed by Peripolli et al. (2017) in cattle populations which showed lower σ^2(f) values than in the Lidia breed. Also, recently Zhang et al. (2015) concluded that the estimator based on pedigree data was moderately correlated with estimators based on ROH when a pedigree is relatively complete. Two main reasons could explain our correlation coefficients; (1) the use of Spearman's rank correlation coefficient instead of simple Pearson's correlation (dictated by the data distribution being different than normal) and (2) low pedigree depth, pedigree accounts only for inbreeding that occurred since pedigree records began. Silio et al. (2013) found correlations > 0.7 in a Spanish pig population with pedigree back to the founder animals of 26 generations.

5. Conclusions

In this study we compared different inbreeding coefficients and diversity parameters estimated with different sources of information (pedigree, microsatellites and SNPs). The correlations among the different parameters estimated with microsatellites (0.99) or SNPs (0.82-1) shown high values and as a consequence similar correlations with F_P. The lowest correlation (0.25) with pedigree inbreeding coefficients was obtained when microsatellite markers are used, while the highest correlation (0.5) was obtained with the $F_{ROH>16\,MB}$ estimates. The remarkable differences between the expected and the observed correlations among molecular and pedigree inbreeding coefficients could be explained by the pedigree depth. Also, the reproductive isolation among Lidia lineages justifies the absence of ID in the molecular markers and as a consequence the low genetic correlation among molecular diversity parameters and pedigree inbreeding coefficients.

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