Revised: 26 June 2020

ORIGINAL ARTICLE

Networks of inbreeding coefficients in a selected population of rabbits

Silvia T. Rodríguez-Ramilo¹ Antonio Reverter² | Juan P. Sánchez³ | Jesus Fernández⁴ | Maria Velasco-Galilea³ | Olga González³ | Miriam Piles³

 ¹GenPhySE, Université de Toulouse, INRAE, ENVT, Castanet Tolosan, France
 ²CSIRO Agriculture & Food, Brisbane, QLD, Australia
 ³IRTA, Caldes de Montbui, Spain
 ⁴INIA, Madrid, Spain

Correspondence

Silvia T. Rodríguez-Ramilo, GenPhySE, Université de Toulouse, INRAE, ENVT, F-31326 Castanet Tolosan, France. Email: silvia.rodriguez-ramilo@inrae.fr

Funding information

Horizon 2020, Grant/Award Number: 633531 and RTA2014-00015-C2-01

Abstract

The correlation between pedigree and genomic-based inbreeding coefficients is usually discussed in the literature. However, some of these correlations could be spurious. Using partial correlations and information theory, it is possible to distinguish a significant association between two variables which is independent from associations with a third variable. The objective of this study is to implement partial correlations and information theory to assess the relationship between different inbreeding coefficients using a selected population of rabbits. Data from pedigree and genomic information from a 200K SNP chip were available. After applying filtering criteria, the data set comprised 437 animals genotyped for 114,604 autosomal SNP. Fifteen pedigree- and genome-based inbreeding coefficients were estimated and used to build a network. Recent inbreeding coefficient based on runs of homozygosity had 9 edges linking it with different inbreeding coefficients. Partial correlations and information theory approach allowed to infer meaningful associations between inbreeding coefficients and highlighted the importance of the recent inbreeding based on runs of homozygosity, but a good proxy of it could be those pedigree-based definitions reflecting recent inbreeding.

KEYWORDS

inbreeding, information theory, partial correlation, rabbit

1 | INTRODUCTION

The coefficient of inbreeding is defined as the probability that two alleles at a given locus are identical by descent (IBD) and occurs when related individuals are mated (Malécot, 1948). One of the most important consequences of the rise of inbreeding is the reduction in the mean of a trait with economic interest (Falconer & Mackay, 1996). Therefore, obtaining accurate estimates of inbreeding is important for the management of animal populations under selection.

Traditionally, inbreeding coefficients have been estimated in animal populations from pedigree records. With pedigree data, it is also possible to distinguish recent from ancient inbreeding by using deterministic or stochastic methods. However, genomic inbreeding coefficients can be obtained nowadays since the cost of genotyping is no longer a limiting factor. Single nucleotide polymorphisms (SNP) are the most commonly used genomic markers due to their automated and accurate genotyping, and refined pedigree-free inbreeding coefficients based on them have been proposed (McQuillan et al., 2008). Genomic inbreeding coefficients account for Mendelian sampling variance (Hill & Weir, 2011) and do not depend on quality and completeness of the pedigree. Therefore, they are expected to be more accurate than pedigree-based coefficients. Among the former, those obtained from the proportion of the genome covered by homozygous regions called runs of homozygosity (ROH) allow to distinguish recent from ancient inbreeding (Pryce, Haile-Mariam, Goddard, & Hayes, 2014).

Correlations between genome- and pedigree-based inbreeding coefficients are usually provided in the literature (e.g. Pryce et al., 2014; Rodríguez-Ramilo, Elsen, & Legarra, 2019; Silió et al., 2013). However, when two inbreeding coefficients (A and B) evolve similarly along generations, it is expected a strong relationship between them. Accordingly, the change of inbreeding coefficient A is linked to the change of inbreeding coefficient B, and vice versa. However, occasionally the association could be coincidental or caused by a third inbreeding coefficient C that affects the first two inbreeding coefficients. In other words, given three inbreeding coefficients (A, B and C), if there is a strong correlation between AC and BC, the correlation AB is likely to be also strong. However, the correlation AB could be non-meaningful or dependents on the correlations AC and BC. This is called a spurious correlation. The occurrence of this kind of correlations can increase with the augmentation of the definition of different inbreeding coefficients. This highlights the importance of assessing spurious correlations.

In order to identify significant associations between two variables that are independent from a third one, Reverter and Chang (2008) suggested an approach that uses first-order partial correlation coefficients combined with information theory (PCIT) methodology. The objective of this study was to detect significant associations between different inbreeding coefficients in a selected population of rabbits using a PCIT algorithm.

2 **MATERIALS AND METHODS**

2.1 **Ethical statement**

The current study was carried out under a Project License from the IRTA Scientific Ethic Committee. Animal manipulations were performed according to the Spanish Policy for Animal Protection, which meets the European Union Normative.

2.2 Data

Animals in the study are a sample of the Caldes line, which belongs to IRTA. This line was founded in 1983 by crossing animals from five New Zealand White lines and a California × New Zealand synthetic line. It has been selected for litter weight and individual growth rate until 1992, for growth rate until 2011. From 2011 to 2016,

no selection was performed on these animals (see Piles et al., 2017 for more details). Management of rabbits was performed avoiding matings between animals with common grandparents. The line is currently in its 60th generation. The average number of animals per generation was 2,928 with a minimum of 1,351 and a maximum of 5,016 individuals. The average number of does per generation was 179 ranging from 117 to 364 dams. The average number of sires per generation was 60, ranging from 37 to 97 sires. The mean generation interval was 292 days, and the 0.05 and 0.95 quartiles of the absolute value of the age difference of dam and sire was 1 to 310 days, respectively. The pedigree file comprised 173,485 animals, with 1,799 sires and 8,082 dams from generation 1 to generation 60. The pedigree was complete and only individuals from the base generation had unknown parents.

DNA was extracted from blood samples from N = 437rabbits born in 2013, 2014 and 2016 (corresponding to generations 49, 50, 51 and 54). Genotyping was performed using the Axiom rabbit array of 200,000 SNP (Affymetrix). No pruning of SNP for linkage disequilibrium was performed, and after the exclusion of SNP with a minor allele frequency (MAF) < 0.05, 114,604 autosomal SNP were available.

Inbreeding computation from pedigree 2.3

Following Ragab, Sánchez, and Baselga (2015), we defined F_{u}^{t} as the inbreeding of an animal from generation u considering generation *t* as the base generation, being t < u. For t = 0, F_{μ}^{0} represents the inbreeding accumulated since the foundation of the line, which is divided into several components that account for the inbreeding accumulated during different periods of time. Thus, for two given generations t_1 and t_2 , being $0 < t_1 < t_2 < u$, we defined the inbreeding accumulated until generation t_1 as F_{0,t_1}^0 , the inbreeding accumulated from generation t_1 to generation t_2 as F_{t_1,t_2}^0 and the inbreeding accumulated from generation t_2 to generation u as $F_{t_2u}^0$. These components are computed from the following formulas derived from the equation for inbreeding in hierarchically structured populations (Wright, 1922):

$$1 - F_{u}^{0} = \left(1 - F_{0,ti}^{0}\right) \left(1 - F_{u}^{ti}\right) \text{ for } i = 1, 2$$

Thus,

$$1 - F_{u}^{0} = 1 - F_{u}^{ti} - F_{0,ti}^{0} + F_{0,ti}^{0} F_{u}^{ti}$$
(Formula 1)

$$F_{u}^{0} = F_{u}^{ti} - F_{0,ti}^{0} \left(1 - F_{u}^{ti}\right)$$

$$F_{0,ti}^{0} = \frac{\left(F_{u}^{0} - F_{u}^{ti}\right)}{\left(1 - F_{u}^{ti}\right)}$$

and

$$\begin{aligned} 1 - F_{u}^{0} &= 1 - F_{0,ti}^{0} - F_{ti,u}^{0} = \left(1 - F_{0,ti}^{0}\right) \left(1 - F_{u}^{ti}\right) & \text{(Formula 2)} \\ F_{ti,u}^{0} &= \left(1 - F_{0,ti}^{0}\right) - \left(1 - F_{0,ti}^{0}\right) \left(1 - F_{u}^{ti}\right) \\ F_{ti,u}^{0} &= \left(1 - F_{0,ti}^{0}\right) \left[1 - \left(1 - F_{u}^{ti}\right)\right] = \left(1 - F_{0,ti}^{0}\right) F_{u}^{ti} \end{aligned}$$

The part of F_u^0 accumulated between generations t_1 and t_2 corresponds to:

$$F_{t1,t2}^{0} = F_{t1,u}^{0} - F_{t2,u}^{0} = F_{0,t2}^{0} - F_{0,t}^{0}$$

 F_u^0 , F_u^{t1} and F_u^{t2} were computed using the program inbupgf90 that implements the algorithm developed by Aguilar and Misztal (2008). $F_{0,t1}^0$, $F_{0,t2}^0$ and $F_{t1,t2}^0$ were computed from the Formulas 1 and 2. Finally, $F_{t1,u}^0 = F_u^0 - F_{0,t1}^0$ and $F_{t2,u}^0 = F_u^0 - F_{0,t2}^0$.

Three periods of 20 generations were considered, and $t_1 = 20$ and $t_2 = 40$. The recent pedigree-based inbreeding coefficient (FpedR) is the inbreeding accumulated in the period immediately preceding individual birth, the intermediate pedigree-based inbreeding coefficient (FpedI) is the inbreeding accumulated during the 20 generations period before this, and the ancient pedigree-based inbreeding coefficient (FpedA) is the inbreeding accumulated during the first 20 generations period of time. An animal born before generation 20 has only accumulated *FpedR*, calculated as F_{μ}^{0} , whereas FpedI and FpedA are set to 0. An animal born between generations 20 and 40 has accumulated FpedR, calculated as $F_{20,\mu}^0 = F_{\mu}^0 - F_{0,20}^0$, and *FpedI*, calculated as $F_{0,20}^0$, whereas FpedA is set to 0. An individual born after generation 40 has accumulated *FpedR* calculated as $F_{40,u}^0 = F_u^0 - F_{0,40}^0$, *FpedI* calculated as $F_{20,40}^0 = F_{0,40}^0 - F_{0,20}^0$, and *FpedA* calculated as $F_{0.20}^0$. Inbreeding coefficients with all pedigree information were also calculated (*FpedAll*).

The software "Grain" (Baumung et al., 2015) version 2.2 (Doekes et al., 2020) was used to calculate the ancestral inbreeding coefficients and the ancestral history coefficient (see below their definitions). The correlation between the inbreeding coefficients calculated using the deterministic recursive algorithm proposed by Aguilar and Misztal (2008) with all the genealogy (FpedAll) and the ones obtained with the stochastic gene dropping process (Baumung et al., 2015) (FpedAllDrop) was high (0.9) with 800,000 replications (gene drops). Consequently, only results from FpedAll will be shown. The ancestral inbreeding coefficient defined by Ballou (1997) was also calculated (Fbal). This coefficient can be defined as the probability that any allele in an individual has been IBD in previous generations at least once. Alternatively, the ancestral inbreeding coefficient according to Kalinowski, Hedrick, and Miller (2000) (Fkal) represents the probability that any allele in an individual is currently IBD and has been IBD in previous generations at least once. It is also possible to calculate the recent inbreeding (FpedRDrop) as the part of the classical inbreeding coefficient whereby alleles are IBD for the first time, and it has been calculated as FpedRDrop = FpedAllDrop - Fkal (Doekes et al., 2019). Finally, we computed the ancestral history coefficient (*Ahc*) defined as the number of times that a random allele in an individual has been IBD in the individual's pedigree. Alleles which have experienced inbreeding more often in the past are less likely to be deleterious than alleles which have undergone IBD less often because those alleles have survived to purging, and therefore, it is probably that they have a neutral or even positive effect on the selected traits. Thus, high values of *Fbal*, *Fkal* or *Ahc* are expected to have a positive effect on the phenotype.

ournal of Animal Breeding and Genetics

2.4 | Inbreeding computation from genomic data

Genomic inbreeding coefficients based on runs of homozygosity (Froh) were obtained using PLINK v1.90 software (Chang et al., 2015). The criteria used for defining a ROH were as follows: (a) the minimum number of SNP was 100; (b) the minimum density was 1 SNP per 50 kb; (c) the maximum distance allowed between two consecutive homozygous SNP in a run was 1 Mb; (d) a maximum of five missing genotypes, and (e) one heterozygous genotype within a particular ROH was permitted. The minimum length that constituted a ROH was set to >1.25 and <2.5, >2.5 and <10, and >10 Mb to reflect ancient (*FrohA*), intermediate (FrohI) and recent (FrohR) ROH-based inbreeding coefficients, respectively. These are the ROH minimum sizes that match to 40, 20 and 5 generations from the common ancestor (Curik, Ferenčaković, & Sölkner, 2014), respectively. Recent inbreeding seems to generate long ROH while shorter ROH mainly proceed from IBD segments shared by old ancestors, which were fragmented by recombination along generations (Kirin et al., 2010). Genomic inbreeding coefficients based on runs of homozygosity (Froh) were calculated as.

$$Froh = \frac{\sum L_{roh}}{L_{genome}}$$

where $\sum L_{\text{roh}}$ is the sum of the length of all ROH detected in an animal in bp, and L_{genome} is the total length of the genome in bp covered by SNP and where the criteria used for defining a ROH were fulfilled.

Genomic-based inbreeding coefficients were also calculated as in VanRaden (2008) (*Fvan*). Then, the inbreeding coefficient based on VanRaden (2008) for individual j was estimated from the self-coancestry of individual j as

$$Fvan_{j} = 2f_{jj} - 1 = 2\left(\frac{1}{L}\sum_{l} \frac{(g_{jl} - p_{l})(g_{jl} - p_{l})}{p_{l}(1 - p_{l})}\right) - 1$$

where g_{jl} is half of the number of copies of the reference allele *A* in the locus *l* for individual *j*, p_l is the allele frequency, and *L* is the total number of SNP.

The proportion of homozygous genotypes (*Fsnp*) and the proportion of homozygous SNP for the minor allele (*PHoMA*) were also calculated.

Expressing the genotype compressed file size relative to its uncompressed form is possible to obtain a measure of compression efficiency (CE) as follows:

$$CE = \frac{Sb - Sa}{Sb}$$

where *Sb* and *Sa* represent the size of the SNP genotype file in bytes before and after compression, respectively. This relates to the order and proportion of homozygote and heterozygote SNP positions (Hudson et al., 2014).

2.5 | Identification of correlations and network reconstitution

Pearson's correlation coefficients and first-order partial correlation coefficients combined with an approximation of information theory (Reverter and Chang, 2008) were used to identify significant associations between the different inbreeding coefficients. The first-order partial correlation coefficients together with a similarity of information theory were calculated with the software PCIT (Watson-Haigh et al., 2010). The PCIT algorithm contains two distinct steps as follows:

2.5.1 | Partial correlations

For every trio of inbreeding coefficients, x, y and z, the three first-order partial correlation coefficients are computed as

$$r_{xy,z} = \frac{r_{xy} - r_{xz}r_{yz}}{\sqrt{\left(1 - r_{xz}^2\right)\left(1 - r_{yz}^2\right)}}$$

and similarly for $r_{xz,y}$ and $r_{yz,x}$.

The partial correlation coefficient between x and y given z (here denoted by $r_{xy,z}$) indicates the strength of the linear relationship between x and y that is independent of (uncorrelated with) z. Calculating the ordinary (or unconditional or zero-order) correlation coefficient (r_{xy} , r_{xz} and r_{yz}) and comparing it with the partial correlation, it is possible to see whether the association between the two inbreeding coefficients has been sharply reduced after eliminating the effect of the third inbreeding coefficient.

2.5.2 | Information theory

For every trio of inbreeding coefficients, and in order to obtain the tolerance level (ε) to be used as the local threshold for capturing significant associations, the mean ratio of partial to direct correlation is calculated as:

$$\varepsilon = \frac{1}{3} \left(\frac{r_{xy,z}}{r_{xy}} + \frac{r_{xz,y}}{r_{xz}} + \frac{r_{yz,x}}{r_{yz}} \right).$$

In the context of the network reconstruction, a connection or edge between inbreeding coefficients *x* and *y* is discarded if:

$$\left| r_{xy} \right| \le \left| \varepsilon \times r_{xz} \right|$$
 and $\left| r_{xy} \right| \le \left| \varepsilon \times r_{yz} \right|$

Otherwise, the association is defined as significant, and a connection or edge between the pair of inbreeding coefficients is established.

Once Pearson's correlations and the significant associations were identified, and the analysis of inbreeding coefficients networks and its visualization were performed with the software Cytoscape 2.8.3 (Shannon et al., 2003).

3 | **RESULTS AND DISCUSSION**

The estimates of the different inbreeding coefficients and their associations in a selected rabbit population were compared. Table 1 shows the descriptive statistics for the different inbreeding coefficients. Average values for pedigree-based inbreeding coefficients (FpedA, FpedI and FpedR) decreased from ancient to recent inbreeding. However, no similar tendency was observed for ROH-based inbreeding coefficients, where the intermediate coefficients (FrohI) showed the highest mean value compared with the ancient (FrohA) and the recent (FrohR). This is probably because the majority of ROH fell into the intermediate category. However, it should be noted that some parameters used for the definition of a ROH and the thresholds imposed during the filtering of the genotypic data can influence the number and length of ROH (Howrigan, Simonson, & Keller, 2011). Accordingly, the number of allowed heterozygous genotypes (Mastrangelo et al., 2016), and the density of the SNP chip and the frequency of SNP genotyping errors (Ferenčaković, Sölkner, & Curik, 2013) can affect Froh. In addition, linkage disequilibrium, recombination and mutation rate can influence the frequency, size and location of ROH (Gibson, Newton, & Collins, 2006).

As expected, the mean *Fkal* was significantly lower than the mean *Fbal*. When comparing recent inbreeding

TABLE 1 Descriptive statistics for the different inbreeding coefficients

Matuia	Moon	Standard	Minimum	Marimum
Metric	Mean	error	wiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiii	Maximum
FpedA	0.0674	0.0000	0.0674	0.0674
FpedI	0.0535	0.0000	0.0519	0.0547
FpedR	0.0250	0.0010	0.0065	0.1615
FpedAll	0.1459	0.0010	0.1272	0.2824
Fbal	0.8546	0.0007	0.8246	0.8819
Fkal	0.1414	0.0009	0.1221	0.2632
FpedRDrop	0.0054	0.0001	0.0029	0.0200
Ahc	2.7155	0.0088	2.3773	3.0936
FrohA	0.0364	0.0003	0.0191	0.0581
FrohI	0.1485	0.0009	0.0727	0.2043
FrohR	0.0749	0.0017	0.0000	0.2347
Fvan	0.0299	0.0033	-0.1414	0.3521
Fsnp	0.6327	0.0009	0.5884	0.7231
PHoMA	0.1063	0.0004	0.0803	0.1446
CE	0.8458	0.0003	0.8145	0.8584

Abbreviations: FpedA, ancient pedigree-based inbreeding coefficient; FpedI, intermediate pedigree-based inbreeding coefficient; FpedR, recent pedigreebased inbreeding coefficient; FpedAll, pedigree-based inbreeding coefficient from all the genealogy; Fbal, pedigree-based inbreeding coefficient from Ballou (1997); Fkal, pedigree-based inbreeding coefficient from Kalinowski et al. (2000); FpedRDrop, recent pedigre-based inbreeding coefficient calculated from gene drop; Ahc, ancestral history coefficient; FrohA, ancient ROH-based inbreeding coefficient; FrohI, intermediate ROH-based inbreeding coefficient; FrohR, recent ROH-based inbreeding coefficient; Fvan, inbreeding coefficient from VanRaden (2008); Fsnp, proportion of homozygous SNP; PHoMA, proportion of homozygous SNP for the minor allele; CE, compression efficiency.

coefficients, the mean FpedRDrop was lower than FpedR, and this one was lower than FrohR.

The genomic coefficients not related with ROH were very different. The mean values were 0.03, 0.11, 0.63 and 0.85 for Fvan, PHoMA, Fsnp and CE, respectively. The average Fsnp (0.63) was much higher than the different *Fped* (ranging between 0.01 and 0.15) because the latter refers to a base population where no homozygosity exists. Thus, in Fsnp alleles that are IBD and identical by state (IBS) cannot be distinguished. Several approaches have been proposed to express the proportion of homozygous SNP in the same scale as pedigree-based coefficients (Toro, García-Cortés, & Legarra, 2011) but they (e.g. Fvan) require the knowledge of the base population allele frequencies. However, given that these frequencies are usually unknown, usually the allele frequencies of the studied population are used providing, generally, inaccurate inbreeding estimates (Toro et al., 2002). In addition, the different approaches are equivalent to move the base population several generations ago (Fsnp), the present (Fvan), to the most ancient ancestors known (Fped) or

Animal Breeding and Genetics

to different intermediate points with different ROH lengths (Morales-Gonzalez et al., 2020).

Emphasis in the partitioning of the inbreeding coefficients based on the distance to a common ancestor has been performed both for pedigree- and genomic-based inbreeding coefficients. This is important because inbreeding arising from a distant common ancestor should has less effect on fitness and economically important related traits compared with inbreeding from a recent common ancestor because natural and artificial selection along time should act to purge deleterious alleles from the population (Holt, Meuwissen, & Vangen, 2005).

Figure 1 shows that the highest Pearson's correlations between pedigree-based inbreeding coefficients were observed between FpedR, FpedAll, Fkal, FpedRDrop and Ahc. Within the genome-based inbreeding coefficients, the highest Pearson's correlations were obtained between FrohR, Fsnp, PHoMA and CE. Moderate Pearson's correlations (between 0.32 and 0.45) were observed between the pedigree-based inbreeding coefficients *FpedR*, *FpedAll*, *Fkal* and *FpedRDrop*, and the genome-based inbreeding coefficients FrohR, Fsnp and PHoMA.

The network between the different evaluated inbreeding coefficients is difficult to interpret from Pearson's correlations even when positive and negative edges are represented separately (Figure 2) because there were 105 different edges linking the different inbreeding coefficients.

Different studies show the correlation between pedigreeand genomic-based inbreeding coefficients. For example, strong correlations between pedigree and genomic-based inbreeding coefficients have been reported in human populations with complete and reliable pedigree (McQuillan et al., 2008). High correlations were also detected in cattle populations with complete generation equivalent values larger than 5 (Doekes et al., 2019; Purfield, Berry, McParland, & Bradley, 2012).

The use of partial correlation and information theory on inbreeding coefficients is novel, and the network from PCIT allowed clarifying the relation between the different tested inbreeding coefficients (Figure 3). Thirty-three significant edges were detected in Figure 3.

Genomic-based inbreeding coefficients were not correlated with their corresponding pedigree-based inbreeding coefficients, except for the case of recent inbreeding. Significant and positive correlations were detected for FpedAll, FpedRDrop and FpedR. This cluster also included significant and positive correlations with some genomic-based inbreeding coefficients such as FrohR, Fsnp, PHoMA, Fvan and CE. Fvan is mostly correlated with PHoMA suggesting that Fvan is giving more importance to minor allele frequencies. In fact, the method 2 from VanRaden (2008) has been implemented to estimate Fvan, and it has been suggested that loci with lower MAF get 6 WILEY Animal Breeding and Genetics

															Γ	1
FpedA					•	•		·				•		0		
0.2	Fpedl		٠		•	•						- 1	•		- c).8
0.02	-0.11	FpedR									•					
0.03	-0.09	1	FpedAll												- 0	.6
-0.01	-0.02	0.31	0.31	Fbal	•			•		•	•	•	•		- c).4
0.04	-0.08	0.9	0.9	0.36	Fkal		•				•			•		
0.04	-0.1	0.79	0.79	-0.11	0.88	pedRDro	p 🔴				•			0	- 0	1.2
-0.01	-0.03	0.3	0.3	0.99	0.35	-0.11	Ahc				0	•			-	0
-0.03	0.01	-0.17	-0.17	0.03	- <mark>0.17</mark>	-0.19	0.04	FrohA	•		•	•				
0	0.03	0.01	0.01	-0.01	-0.01	0	-0.02	-0.09	Frohl	•				۲	().2
0.08	-0.03	0.44	0.44	0.08	0.39	0.37	0.07	-0.31	-0.16	FrohR					(0.4
-0.03	0.02	0.21	0.21	-0.03	0.15	0.15	-0.04	-0.05	-0.08	0.22	Fvan			•		
0.05	-0.02	0.45	0.45	0.06	0.38	0.37	0.06	-0.17	0.31	0.8	0.27	Fsnp			().6
0	-0.04	0.39	0.39	-0.03	0.32	0.34	-0.02	-0.11	-0.02	0.52	0.69	0.58	PHoMA		(0.8
0.05	-0.07	0.11	0.11	0.16	0.11	0.04	0.17	-0.22	0.11	0.55	-0.08	0.43	0	CE		

FIGURE 1 Heat map of Pearson's correlation coefficients among the different inbreeding coefficients. Above the diagonal: blue indicates strong positive correlation, white illustrates no correlation and red denotes strong negative correlation. Below the diagonal: correlation values. *FpedA*: Ancient pedigree-based inbreeding coefficient; *FpedI*: Intermediate pedigree-based inbreeding coefficient; *FpedR*: Recent pedigree-based inbreeding coefficient; *FpedI*: Pedigree-based inbreeding coefficient; *FpedR*: Recent pedigree-based inbreeding coefficient from all the genealogy; *Fbal*: Pedigree-based inbreeding coefficient from Ballou (1997); *Fkal*: Pedigree-based inbreeding coefficient from Kalinowski et al. (2000); *FpedRDrop*: recent pedigree-based inbreeding coefficient; *FrohA*: Ancient ROH-based inbreeding coefficient; *FrohI*: Intermediate ROH-based inbreeding coefficient; *FrohR*: Recent ROH-based inbreeding coefficient; *Fvan*: Inbreeding coefficient from VanRaden (2008); *Fsnp*: Proportion of homozygous SNP; *PHoMA*: Proportion of homozygous SNP for the minor allele; CE: compression efficiency

higher weight in method 2 than in VanRaden's method 1 (Toro et al., 2011).

Interestingly, *Fkal* was also comprised in this group and non-significant correlations were observed between *Fkal* and *Fbal* or *Ahc*. Parland, Kearney, and Berry (2009) indicated that the correlation between *Fkal* and *Fbal* was weak, ranging from 0.28 to 0.38. Also Schäler, Krüger, Thaller, and Hinrichs (2020) suggested that this correlation was small (0.22), indicating that the two coefficients are measuring different population statistics. The correlation between *Fbal* and *Ahc* was positive and strong, as well as those between both of them and *CE*. *FpedRDrop* coefficient was negatively correlated with *FpedI*.

Correlations between inbreeding coefficients vary between studies. Both, population structure and introgression seem important factors affecting this variability found in the literature (e.g. Schäler et al., 2020). It seems that commercial lines present a high and positive correlation for *FpedAll*



FIGURE 2 Network of Pearson's correlation coefficients for different inbreeding estimates. Blue edges show the positive correlations and red edges the negative ones. *FpedA*: Ancient pedigree-based inbreeding coefficient; *FpedI*: Intermediate pedigree-based inbreeding coefficient; *FpedR*: Recent pedigree-based inbreeding coefficient; *FpedAll*: Pedigree-based inbreeding coefficient from all the genealogy; *Fbal*: Pedigree-based inbreeding coefficient from Ballou (1997); *Fkal*: Pedigree-based inbreeding coefficient from Kalinowski et al. (2000); *FpedRDrop*: recent pedigree-based inbreeding coefficient calculated from gene drop; *Ahc*: Ancestral history coefficient; *FrohA*: Ancient ROH-based inbreeding coefficient; *FrohR*: Recent ROH-based inbreeding coefficient; *FrohR*: Recent ROH-based inbreeding coefficient from VanRaden (2008); *Fsnp*: Proportion of homozygous SNP; *PHoMA*: Proportion of homozygous SNP for the minor allele; CE: compression efficiency

and *Fkal* (0.90 in the present study), whereas lines with introgression or local lines show a small correlation between *FpedAll* and *Fkal*. In addition, the correlation between *FpedAll* and *Fbal* is higher within local or introgressed lines (Schäler et al., 2020). However, further research on correlations is needed to validate such statements. In addition, the inbreeding coefficient *FrohA* was negatively correlated with *FrohR* and *CE*. *FrohR* was the central coefficient having 9 edges that link it to different inbreeding coefficients and, as expected, it is negatively correlated with *FrohA*. *FpedI* was negatively correlated with *FpedRDrop* and *Fkal*.



FIGURE 3 Network of significant associations obtained from PCIT for different inbreeding estimates. Blue edges show the positive correlations and red edges the negative ones. FpedA: Ancient pedigreebased inbreeding coefficient; FpedI: Intermediate pedigree-based inbreeding coefficient; FpedR: Recent pedigree-based inbreeding coefficient; FpedAll: Pedigreebased inbreeding coefficient from all the genealogy; Fbal: Pedigree-based inbreeding coefficient from Ballou (1997); Fkal: Pedigree-based inbreeding coefficient from Kalinowski et al. (2000); FpedRDrop: recent pedigree-based inbreeding coefficient calculated from gene drop; Ahc: Ancestral history coefficient; FrohA: Ancient ROHbased inbreeding coefficient; FrohR: Recent ROH-based inbreeding coefficient; Fvan: Inbreeding coefficient from VanRaden (2008); Fsnp: Proportion of homozygous SNP; PHoMA: Proportion of homozygous SNP for the minor allele; CE: compression efficiency

The PCIT approach allows inferring meaningful associations between inbreeding coefficients and emphasizes the importance of *FrohR* from other coefficients. In order to limit the increase in inbreeding in a population under selection or not, it could be recommended to monitor this coefficient, but a good proxy of it could be those pedigree-based definitions reflecting recent inbreeding (*FpedR* and *FpedRDrop*).

ACKNOWLEDGEMENTS

This study was supported by the European Unions' Horizon 2020 Research & Innovation programme under grant agreement N° 633531 – FEED-A-GENE. This work was also supported by INIA (RTA2014-00015-C2-01) and GDivSelGen action (INRA SelGen metaprogram). Support from the CSIRO-INRA Linkage Grant is gratefully acknowledged. Authors are also grateful to the GenoToul bioinformatics platform Toulouse Midi-Pyrenees for providing computing and storage resources.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data will be available upon reasonable request.

ORCID

Silvia T. Rodríguez-Ramilo https://orcid. org/0000-0001-7150-0692 *Juan P. Sánchez* https://orcid.org/0000-0001-8639-6146

REFERENCES

- Aguilar, I., & Misztal, I. (2008). Recursive algorithm for inbreeding coefficients assuming non-zero inbreeding of unknown parents. *Journal of Dairy Science*, 91, 1669–1672. https://doi.org/10.3168/ jds.2007-0575
- Ballou, J. D. (1997). Ancestral inbreeding only minimally affects inbreeding depression in mammalian populations. *Journal of Heredity*, 88, 169–178. https://doi.org/10.1093/oxfordjournals. jhered.a023085
- Baumung, R., Farkas, J., Boichard, D., Mészáros, G., Sölkner, J., & Curik, I. (2015). GRAIN: A computer program to calculate ancestral and partial inbreeding coefficients using a gene dropping approach. *Journal of Animal Breeeding and Genetics*, 132, 100–108. https:// doi.org/10.1111/jbg.12145

- Chang, C. C., Chow, C. C., Tellier, L. C. A. M., Vattikuti, S., Purcell, S. M., & Lee, J. J. (2015). Second-generation PLINK: Rising to the challenge of larger and richer datasets. *Gigascience*, 4, 7. https://doi. org/10.1186/s13742-015-0047-8
- Curik, I., Ferenčaković, M., & Sölkner, J. (2014). Inbreeding and runs of homozygosity: A possible solution to an old problem. *Livestock Science*, 166, 26–34. https://doi.org/10.1016/j.livsci.2014.05.034
- Doekes, H. P., Curik, I., Nagy, I., Farkas, J., Kövér, G., & Windig, J. J. (2020). Revised calculation of Kalinowski's ancestral and new inbreeding coefficients. *Diversity*, 12, 155. https://doi.org/10.3390/ d12040155
- Doekes, H. P., Veerkamp, R. F., Bijma, P., de Jong, G., Hiemstra, S. J., & Windig, J. J. (2019). Inbreeding depression due to recent and ancient inbreeding in Dutch Holstein-Friesian dairy cattle. *Genetics Selection Evolution*, 51, 54. https://doi.org/10.1186/s1271 1-019-0497-z
- Falconer, D. S., & Mackay, T. F. C. (1996). Introduction to quantitative genetics (4th ed.). UK: Benjamin Cummings.
- Ferenčaković, M., Sölkner, J., & Curik, I. (2013). Estimating autozygosity from high-throughput information: Effects of SNP density and genotyping errors. *Genetics Selection Evolution*, 45, 42. https://doi. org/10.1186/1297-9686-45-42
- Gibson, J., Newton, E. M., & Collins, A. (2006). Extended tracts of homozygosity in outbred human populations. *Human Molecular Genetics*, 15, 789–795. https://doi.org/10.1093/hmg/ddi493
- Hill, W. G., & Weir, B. S. (2011). Variation in actual relationship as a consequence of Mendelian sampling and linkage. *Genetics Research*, 93, 47–64. https://doi.org/10.1017/S001667231 0000480
- Holt, M., Meuwissen, T. H. E., & Vangen, O. (2005). The effect of fast created inbreeding on litter size and body weights in mice. *Genetics Selection Evolution*, 37, 523–537. https://doi.org/10.1051/ gse:2005014
- Howrigan, D. P., Simonson, M. A., & Keller, M. C. (2011). Detecting autozygosity through runs of homozygosity: A comparison of three autozygosity detection algorithms. *BMC Genomics*, 12, 460. https:// doi.org/10.1186/1471-2164-12-460
- Hudson, N. J., Porto-Neto, L. R., Kijas, J., McWilliam, S., Taft, R. J., & Reverter, A. (2014). Information compression exploits patterns of genome composition to discriminate populations and highlight regions of evolutionary interest. *BMC Bioinformatics*, 15, 66. https:// doi.org/10.1186/1471-2105-15-66
- Kalinowski, S. T., Hedrick, P. W., & Miller, P. S. (2000). Inbreeding depression in the Speke's Gazelle captive breeding program. *Conservation Biology*, 14, 1375–1384. https://doi. org/10.1046/j.1523-1739.2000.98209.x
- Kirin, M., McQuillan, R., Franklin, C. S., Campbell, H., McKeigue, P. M., & Wilson, J. J. (2010). Genomic runs of homozygosity record population history and consanguinity. *PLoS One*, *5*, e13996. https:// doi.org/10.1371/journal.pone.0013996
- Malécot, G. (1948). *Les mathématiques de l'hérédité*. France: Masson et Cie.
- Mastrangelo, S., Tolone, M., Gerlando, R. D., Fontanesi, L., Sardina, M. T., & Portolano, B. (2016). Genomic inbreeding estimation in small populations: Evaluation of runs of homozygosity in three local dairy cattle breeds. *Animal Consortium*, 10, 746–754. https://doi. org/10.1017/S1751731115002943
- McQuillan, R., Leutenegger, A., Abdel-Rahman, R., Franklin, C. S., Pericic, M., Barac-Lauc, L., ... Wilson, J. F. (2008). Runs of

homozygosity in European populations. *American Journal of Human Genetics*, 83, 359–372. https://doi.org/10.1016/j.ajhg.2008.08.007

Animal Breeding and Genetics

- Morales-Gonzalez, E., Saura, M., Fernández, A., Fernández, J., Pong-Wong, R., Cabaleiro, S., ... Villanueva, B. (2020). Evaluating different genomic coancestry matrices for managing genetic variability in turbot. *Aquaculture*, 520, 734985. https://doi.org/10.1016/j.aquac ulture.2020.734985
- Parland, S. M., Kearney, F., & Berry, D. P. (2009). Purging of inbreeding depression within the Irish Holstein-Friesian population. *Genetics Selection Evolution*, 41, 16. https://doi. org/10.1186/1297-9686-41-16
- Piles, M., David, I., Ramon, J., Canario, L., Rafel, O., Pascual, M., ... Sánchez, J. P. (2017). Interaction of direct and social genetic effects with feeding regime in growing rabbits. *Genetics Selection Evolution*, 49, 58. https://doi.org/10.1186/s12711-017-0333-2
- Pryce, J. E., Haile-Mariam, M., Goddard, M. E., & Hayes, B. J. (2014). Identification of genomic regions associated with inbreeding depression in Holstein and Jersey dairy cattle. *Genetics Selection Evolution*, 46, 71. https://doi.org/10.1186/s12711-014-0071-7
- Purfield, D. C., Berry, D. P., McParland, S., & Bradley, D. G. (2012). Runs of homozygosity and population history in cattle. *BMC Genetics*, 13, 70. https://doi.org/10.1186/1471-2156-13-70
- Ragab, M., Sánchez, J. P., & Baselga, M. (2015). Effective population size and inbreeding depression on litter size in rabits. A case study. *Journal of Animal Breeding and Genetics*, 132, 68–73. https://doi. org/10.1111/jbg.12110
- Reverter, A., & Chang, E. K. F. (2008). Combining partial correlation and information theory approach to the reversed engineering of gene co-expression networks. *Bioinformatics*, 24, 2491–2497. https://doi. org/10.1093/bioinformatics/btn482
- 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, 4227–4237. https://doi.org/10.3168/ jds.2018-15405
- Schäler, J., Krüger, B., Thaller, G., & Hinrichs, D. (2020). Comparison of ancestral, partial, and genomic inbreeding in a local pig breed to achieve genetic diversity. *Conservation Genetetics Resources*, 12, 77–86. https://doi.org/10.1007/s12686-018-1057-5
- Shannon, P., Markiel, A., Ozier, O., Baliga, N. S., Wang, J. T., Ramage, D., ... Ideker, T. (2003). Cytoscape: A sofware environment for integrated models of biomolecular interaction networks. *Genome Research*, 13, 2498–2504. https://doi.org/10.1101/gr.1239303
- Silió, L., Rodríguez, M. C., Fernández, A., Barragán, C., Benítez, R., Óvilo, C., & Fernández, A. I. (2013). Measuring inbreeding and inbreeding depression on pig growth from pedigree or SNP-derived metrics. *Journal of Animal Breeding and Genetics*, *130*, 349–360. https://doi.org/10.1111/jbg.12031
- Toro, M. A., Barragán, C., Óvilo, C., Rodrigáñez, J., Rodríguez, C., & Silió, L. (2002). Estimation of coancestry in Iberian pigs using molecular markers. *Conservation Genetics*, *3*, 309–320. https://doi. org/10.1023/A:1019921131171
- Toro, M. A., García-Cortés, L. A., & Legarra, A. (2011). A note on the rationale for estimating genealogical coancestry from molecular markers. *Genetics Selection Evolution*, 43, 27. https://doi. org/10.1186/1297-9686-43-27
- VanRaden, P. M. (2008). Efficient methods to compute genomic predictions. *Journal of Dairy Science*, 91, 4414–4423. https://doi. org/10.3168/jds.2007-0980

-WILEY- Animal Breeding and Genetics

10

Watson-Haigh, N. S., Kadarmideen, H. N., & Reverter, A. (2010). PCIT: A R package for weighted gene co-expression networks based on partial correlation and information theory approaches. *Bioinformatics*, 26, 411–413. https://doi.org/10.1093/bioinforma tics/btp674

Wright, S. (1922). Coefficients of inbreeding and relationship. American Naturalist, 56, 330–338. Retrieved from https://www.jstor.org/stabl e/2456273. https://doi.org/10.1086/279872 **How to cite this article:** Rodríguez-Ramilo ST, Reverter A, Sánchez JP, et al. Networks of inbreeding coefficients in a selected population of rabbits. *J Anim Breed Genet*. 2020;00:1–10. <u>https://doi.org/10.1111/jbg.12500</u>