Levels of Inbreeding Derived from Runs of Homozygosity: A Comparison of Austrian and Norwegian Cattle Breeds

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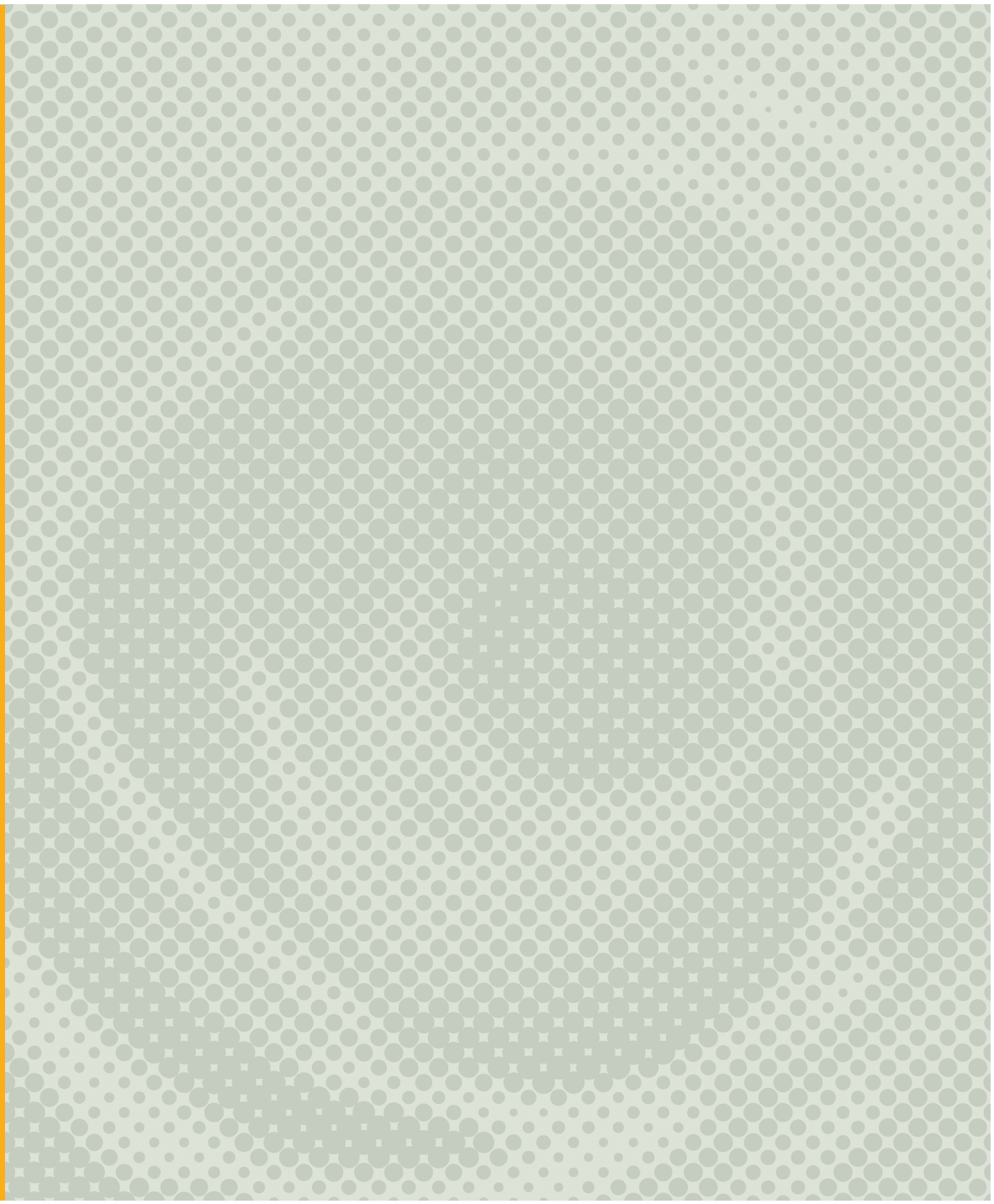

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SUMMARY

Conventionally, levels of inbreeding for livestock animals are estimated analyzing pedigree data. The recent availability of high density SNP arrays for the bovine genome has provided the opportunity for investigation of levels of autozygosity based on runs of homozygosity (ROH). A run of homozygosity is a continuous segment of DNA sequence without heterozygosity in the diploid state. Levels of homozygosity derived from ROH are recognized as potential inbreeding measure in livestock animals. Here we compare levels of homozygosity derived from proportion of ROH in genome (F_{ROH}) and pedigree inbreeding estimates (F_{ped}). We analyzed genotype and pedigree data from 1687 animals from four cattle breeds (Brown Swiss, Norwegian Red, Tyrol Grey and Fleckvieh – dual purpose Simmental). Distribution of ROH was obtained by PLINK software, while proportions of genome in ROH were calculated for five cut-off lengths (1Mb, 2Mb, 4Mb, 8Mb, 16Mb). Pedigree data was analyzed by PEDIG software and inbreeding coefficients for complete pedigree (average complete generation equivalents ranging from 6.46 to 9.02 for the four breeds) and over 5 generations were calculated. Levels of autozygosity from pedigree information were similar to those derived from ROH >8Mb. The strongest correlations with pedigree inbreeding coefficients were obtained between levels of homozygosity derived from ROH for cut-off length of 4Mb (F_{ROH4}) and inbreeding coefficients for complete pedigrees (F_{pedT}) varying from 0.619 for Norwegian Red up to 0.705 for Tyrol Grey. We conclude that proportion of the genome arranged in long homozygous segments provides a good indication of inbreeding levels and that the choice of cut-off lengths of ROH allows determining autozygosity derived from recent or remote ancestors.

Keywords: runs of homozygosity, inbreeding coefficients, pedigree, correlation

INTRODUCTION

An increase of inbreeding level is manifested through loss of genetic variation and emergence of inbreeding depression. Conventionally, inbreeding levels in livestock animals are calculated from pedigree records using methodology originally proposed by Wright (1922). Development of molecular markers provided opportunity for studying inbreeding by measuring loss of heterozygosity. According to this, measures of levels of multilocus heterozygosity were considered as counterparts for inbreeding coefficients (Coltman *et al.* 1999). However it seems that multilocus heterozygosity is a rather poor indicator of inbreeding level. Recently, new measures of inbreeding levels derived from SNP markers, based on variance of genotype values, were introduced by Van Raden (2008) and Yang et al. (2010).

The availability of high density SNP arrays provides the opportunity to scan the bovine genome for runs of homozygosity (ROH). A run of homozygosity (ROH) essentially is a continuous segment of DNA sequence without heterozygosity in the diploid state. Definition of ROH is still not straightforward since different studies used different criteria regarding the minimum length of ROH, number of SNP in ROH and presence of a small number of heterozygote genotypes (Ku *et al.* 2011).

Inbreeding to a common ancestor is considered as the major mechanism for emergence of ROH. Offspring inherits chromosomal segments that are identical-by-descent from both parents. Due to this, long ROH are generated by inbreeding to a recent ancestor while short segments reflect inbreeding from distant generations. A first study focused on runs of homozygosity in the human genome was presented by Broman and Weber (1999); they screened several referenced families to identify long chromosomal segments using microsatellites markers. However ROH did not receive serious attention until first study using SNP array was carried out by Gibson *et al. (2006)*. This was followed by a number of studies using ROH in population genetics studies (Kirin et al., 2010)

(McQuillan et al., 2008) (Nothnagel et al., 2010) as well as for association studies focusing on association between ROH and complex diseases and traits (Lencz et al., 2007). Runs of homozygosity may also be used in animal genetics for estimation of inbreeding levels. Measures of inbreeding based on ROH could then further be used for estimation of inbreeding depression.

One reason to utilize information from ROH for inbreeding estimation is that inbreeding estimates based on pedigree records have several drawbacks. Several studies confirmed that errors in cattle pedigrees are very common (e.g., Ron *et al.* 1996). Pedigree errors appear due to mismothering, misidentification and incorrect recording procedure. In addition, pedigree inbreeding estimates the proportion of the genome that is identical by descent with respect to a rather poorly defined founder generation. Animals in base population are considered to be unrelated causing a failure to capture the influence of relatedness of individuals of this base population. In addition, on average half of gamete's genome has a maternal origin and another half paternal origin but this average has a high variance and it increases with new meiosis (Carothers *et al.* 2006). According to this, pedigree based inbreeding coefficient are not very exact estimates of true levels of inbreeding.

To compare results derived from conventional estimates of inbreeding with those derived from ROH, we calculated levels of autozygosity based on ROH and pedigree inbreeding coefficients in 1687 bulls from four cattle breeds (Brown Swiss, Norwegian Red, Tyrol Grey and Fleckvieh (dual-purpose Simmental)). We correlated measures of homozygosity derived from ROH (F_{ROH}) with pedigree inbreeding coefficients (F_{ped}). Additionally, we used information from ROH profiles and knowledge of breed histories in order to explain their inbreeding past.

MATERIALS AND METHODS

Genotype data from 1687 bulls were obtained and analyzed for ROH. Additionally, pedigree inbreeding coefficients over 5 generations (F_{ped5}) and for complete pedigree were calculated (F_{pedT}). The animals originated from four different cattle breeds: 469 Brown Swiss, 502 Fleckvieh (dual-

purpose Simmental), 217 Tyrol Grey and 499 Norwegian Red.

The pedigree records and genotype data were provided by Geno SA for Norwegian Red and by ZuchtData EDV-Dienstleistungen GmbH for three other breeds. Birth years of genotyped bulls were in range of 1970 – 2006 for Brown Swiss, 1996 – 2004 for Norwegian Red, 2001 – 2004 for Fleckvieh and 1970 – 2006 for Tyrol Grey (Table 1). The completeness of pedigrees was evaluated with the number of complete generation equivalents (Boichard *et al.*, 1997, Sölkner *et al.*, 1998).

Sets of young genotyped animals were selected in case of Fleckvieh and Norwegian Red while for Brown Swiss and Tyrol Grey, genotype data from all animals provided were included in calculations.

Table 1 Total number of animals in pedigree, reference population, average complete generation equivalents, range of birth year and range of birth year (reference population)

Breed	Total number of animals in pedigree	Reference population	Complete generation equivalent	Range of birth years	Range of birth years (reference population)
Brown Swiss	5482	463	8.19 (±1.16)	1925 - 2006	1970 – 2006
Norwegian Red	9921	498	9.02 (± 0.58)	1917 - 2004	1996 – 2004
Tyrol Grey	1647	215	6.46 (± 1.19)	1950 - 2006	1970 – 2006
Fleckvieh	41090	502	7.30 (± 0.41)	1930 - 2010	2001 – 2004

Pedigree data was analyzed with PEDIG software package (Boichard, 2002). Complete generation equivalents and inbreeding coefficients were calculated using *ngen.f* and *vanrad.f* routines of this package. Inbreeding coefficients were calculated taking 5 generations (F_{ped5}) and complete pedigree (F_{pedT}) into account. Average of complete generation equivalents were calculated for genotyped animals of each breed taking into account all known ancestors (Table 1.)

All 1687 animals were genotyped using Illumina Bovine SNP 50k Bead chip technology. Genotype data from all four breeds were merged into one data set. Markers with gc_score lower than 0.2 were excluded from data sets of each breed. Data sets of each breed contained different number of genotypes for SNP markers (Brown Swiss = 51515, Norwegian Red = 47471, Fleckvieh= 51582, Tyrol Grey = 47270). A data set including autosomal SNP markers common for all four cattle

breeds was composed of 42422 SNP markers. Furthermore, SNP markers with minor allele frequency lower than 1% were removed from final data set as well as those with more than 5% missing genotypes. Also, all animals with more than 5% missing genotypes were excluded. Finally, the total number of genotyped individuals in the data set was 1678 while the total number of genotypes for SNP markers was 36273. Quality control was conducted using SAS software v9.1.3 (SAS Institute Inc., 2009) and PLINK (Purcell *et al*., 2007). Runs of homozygosity were detected by PLINK with sliding windows of 1000kb, minimum number of 15 SNP and 5 missing calls; no heterozygous calls were allowed. Maximum gap between two consecutive homozygous SNP was set to 1Mb; otherwise a run of homozygosity was split in two segments.

Individual levels of autozygosity (F_{ROH}) were calculated as the proportion of genome in runs of homozygosity over the overall length of the genome covered by the SNP involved. Size of the genome covered by SNP was calculated using a reference map file derived from all four breeds (2543177.309 kb). Five cut-off lengths were used to calculate proportion of genome covered with ROH (>1Mb, >2Mb, >4Mb, >8Mb, >16Mb). Correlations between levels of homozygosity ($F_{ROH1,}$ F_{ROH2}, F_{ROH4} F_{ROH8}, and F_{ROH16}) and pedigree inbreeding coefficients (F_{ped}) were calculated. In addition, ROH profiles were obtained by plotting number of ROH versus proportion of genome in ROH for five cut-off lengths (>1Mb. >2Mb, >4Mb, >8Mb, >16Mb). ROH profiles were also provided for 100 individuals with extreme F_{pedT} values. We selected 50 animals with minimal F_{pedT} and 50 animals with maximum values F_{pedT}, selecting only animals with a minimum number of 5 complete generation equivalents. Results obtained from PLINK were analyzed using SAS and R (R Development Core Team, 2009). Plots and graphs were made in R.

RESULTS

We calculated F_{ped} and F_{ROH} for 1678 animals from four different breeds. Size and completeness of pedigree records is presented in Table 1. Average complete generation equivalents for genotyped

animals ranged from 6.461 (± 1.189) for Tyrol Grey to 9.025 (± 0.584) for Norwegian Red indicating good quality of pedigree data.

Brown Swiss population was distinguished from the other three breeds in having on average the highest values for all categories of F_{ROH} as well as for F_{pedT} and F_{ped5}. Thus, the average value for F_{ROH1} was 0.142 (±0.036) while averages for F_{ROH8} and F_{ROH16} were 0.066 (±0.031) and 0,033 (±0.024) respectively, almost double compared to the Norwegian Red population who had second highest average value for F_{ROH8} and F_{ROH16} (Table 2). Values for F_{pedT} and F_{ped5} were 0.041 (± 0.022) and 0.0214 (± 0.018), values considerably higher than in the other three breeds (Table 2). In addition, Brown Swiss population had on average the largest number of ROH 92.5 (±10.99) and on average the longest segments 3.88 Mb (±0.77) (Table 3) compared to the other three breeds (see also Figure 1).

Table 2 Mean, standard deviation and range of levels of homozygosity derived from ROH (F_{ROH}) and pedigree inbreeding coefficients for complete pedigree (F_{pedT}) and over 5 generations (F_{ped5})

	Brown Swiss			Norwegian Red		
	Mean	Standard deviation	Range	Mean	Standard deviation	Range
F_{pedT}	0.041	0.022	0 - 0.127	0.021	0.014	0 - 0.095
F_{ped5}	0.021	0.018	0 - 0.107	0.01	0.012	0 - 0.082
F_{ROH1}	0.142	0.036	0.047 - 0.273	0.096	0.025	0.027 - 0.019
F_{ROH2}	0.115	0.036	0.019 - 0.252	0.072	0.025	0.003 - 0.168
F_{ROH4}	0.093	0.035	0.004 - 0.227	0.053	0.024	0 - 0.145
F_{ROH8}	0.066	0.031	0 - 0.194	0.033	0.207	0 - 0.121
F_{ROH16}	0.033	0.024	0 - 0.154	0.015	0.016	0 - 0.09
	Tyrol Grey			Fleckvieh		
	Mean	Standard deviation	Range	Mean	Standard deviation	Range
F_{pedT}	0.024	0.022	0 - 0.167	0.014	0.013	0 - 0.09
F_{ped5}	0.016	0.020	0 - 0.159	0.009	0.012	0 - 0.085
F_{ROH1}	0.078	0.027	0.034 - 0.234	0.085	0.020	0.028 - 0.183
F_{ROH2}	0.053	0.027	0.011 - 0.213	0.052	0.019	0.009 - 0.150
F_{ROH4}	0.041	0.027	0 - 0.203	0.030	0.017	0.002 - 0.124
F_{ROH8}	0.030	0.026	0 - 0.183	0.016	0.016	0 - 0.102
F_{ROH16}	0.016	0.020	0 - 0.140	0.008	0.012	0 - 0.062

Fleckvieh had the lowest F_{ROH} values except for F_{ROH1} = 0.085 (± 0.02). The average pedigree inbreeding coefficients were also the lowest comparing to other three breeds with F_{pedT} = 0.014 (±0.013) and F_{ped5} = 0.009 (± 0.012) (Table 2). Further, Fleckvieh population comparing to other

breeds had on average the shortest ROH length 2.36 Mb (±0.42) while average number of ROH was high, 90.38 (± 12.71) (Table 3).

Figures 1 and 2 provide a visualization of the patterns (number and total length) of ROH in the four breeds. Average value for ROH in category (1 – 2Mb) was over 80Mb for Fleckvieh while values for other three breeds were between 60Mb and 70Mb (Figure 2). For Fleckvieh, averages gradually declined from categories (2 – 4Mb) up to category (>16Mb) (Figure 2).

Table 3 Mean, standard deviation (SD) and range of number of ROH, total length in ROH (>1Mb) and average length of ROH (Mb)

		Number of ROH (>1Mb)	Total length in ROH (Mb) >1Mb	Average length of ROH (Mb)
Brown Swiss	Mean (SD)	92.5 (± 11.0)	360.7 (± 91.2)	3.87 (± 0.77)
	Range	59 – 117	118.8 - 694.7	1.74 - 7.39
Norwegian Red	Mean (SD)	77.2 (± 10.1)	243.9 (± 63.7)	3.14(± 0.64)
	Range	45 – 106	69.7 - 484.5	1.48 - 5.82
Tyrol Grey	Mean (SD)	68.73 (± 9.63)	199.1 (± 68.3)	2.89 (± 0.87)
	Range	48 – 98	85.6 - 595.1	1.64 - 7.62
Fleckvieh	Mean (SD)	90.38 (± 12.71)	214.9 (± 51.5)	2.36 (± 0.42)
	Range	41 – 124	70.1 - 465.6	1.61 - 4.23

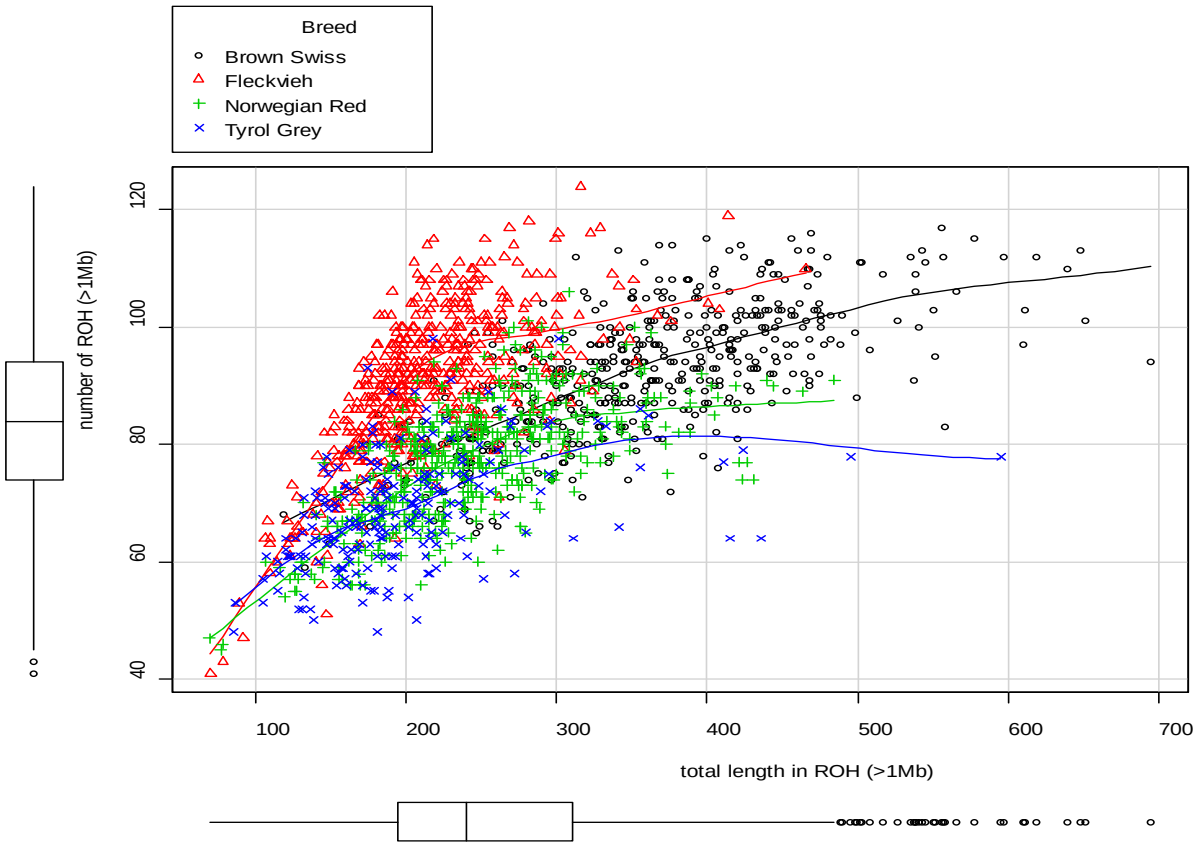

Figure 1 Individual patterns of ROH over 1Mb. The number of ROH compared to the total length in ROH for individuals from four analyzed breeds

Norwegian Red population had considerably higher average only for category (1 – 2 Mb) while other categories showed small variation in average values (Figure 2). Brown Swiss is characterized by very high averages for categories including long segments in comparison to other breeds (Figure 2). Thus, Brown Swiss population had the highest values for categories (8 – 16Mb) and (>16Mb) with average values of over 80Mb for these two categories (Figure 2)

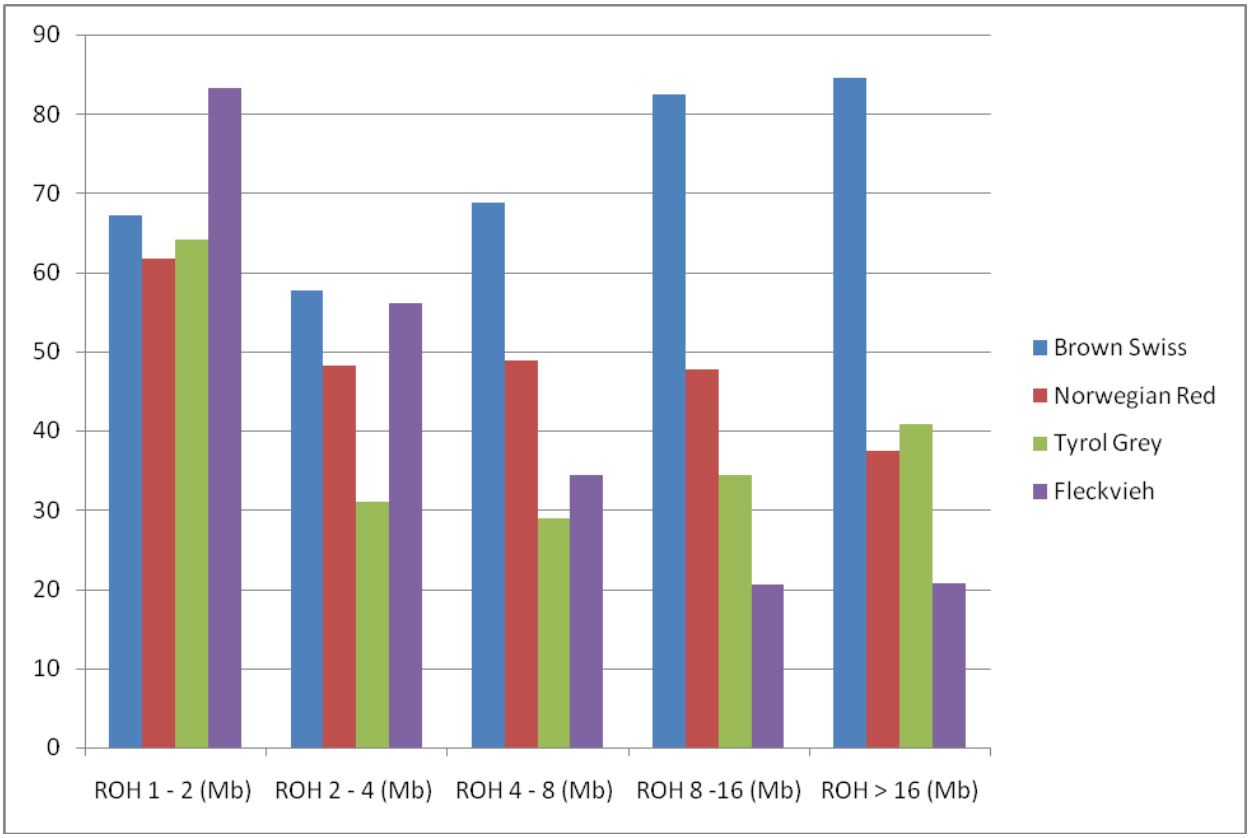

Figure 2 Distribution of ROH in four analyzed breeds. The average total length in ROH in 5 length categories for each breed

Tyrol Grey also had markedly higher proportion of genome covered with ROH in category (1 – 2Mb) while proportion of ROHs increases from category between (4 – 8 Mb) toward category (> 16Mb).

Correlations between F_{ped} and F_{ROH} estimates ranged from r=0,485 between F_{ped5} and F_{ROH1} in case of Norwegian Red to r=0,714 between F_{pedT} and F_{ROH1} in case of Brown Swiss (Table 4).

Generally, correlations between F_{pedT} and F_{ROH} for all cut-off lengths were approximately in same range for all breeds except Norwegian Red population which had somewhat lower correlations (Table 4). Further, F_{pedT} showed higher correlations with F_{ROH} for all cut-off lengths than F_{ped5}. Comparing F_{ROH} and F_{ped} values, the strongest correlations were detected between F_{ROH4} and F_{pedT} across all four breeds varying from r=0,619 for Norwegian Red to r=0.705 for Tyrol Grey.

Table 4 Correlation between pedigree levels of inbreeding (F_{pedT}, F_{ped5}) and levels of homozygosity derived from ROH (F_{ROH})

	Brown Swiss		Fleckvieh		Norwegian Red		Tyrol Grey	
	F_{pedT}	F_{ped5}	F_{pedT}	F_{ped5}	F_{pedT}	F_{ped5}	F_{pedT}	F_{ped5}
F_{pedT}	1.000	0.941	1.000	0.959	1.000	0.940	1.000	0.963
F_{ped5}	0.941	1.000	0.959	1.000	0.940	1.000	0.963	1.000
F_{ROH1}	0.714	0.628	0.649	0.617	0.602	0.485	0.694	0.660
F_{ROH2}	0.713	0.627	0.679	0.652	0.600	0.490	0.701	0.666
F_{ROH4}	0.699	0.625	0.704	0.683	0.619	0.522	0.705	0.681
F_{ROH8}	0.647	0.595	0.699	0.682	0.605	0.530	0.703	0.690
F_{ROH16}	0.563	0.542	0.673	0.661	0.533	0.499	0.670	0.676

ROH profiles of animals with extreme F_{pedT} estimates are shown in Figure 3. The two extreme groups are separated from each other and with regard to ROH profiles. Animals with minimal F_{pedT} had not more than 150Mb of genome in ROH and not more than 20 ROH except one outlier (Figure 3). In contrast, most of the animals with high F_{pedT} had more than 200Mb of their genome in ROH except three animals that had a lower amount of genome in ROH.

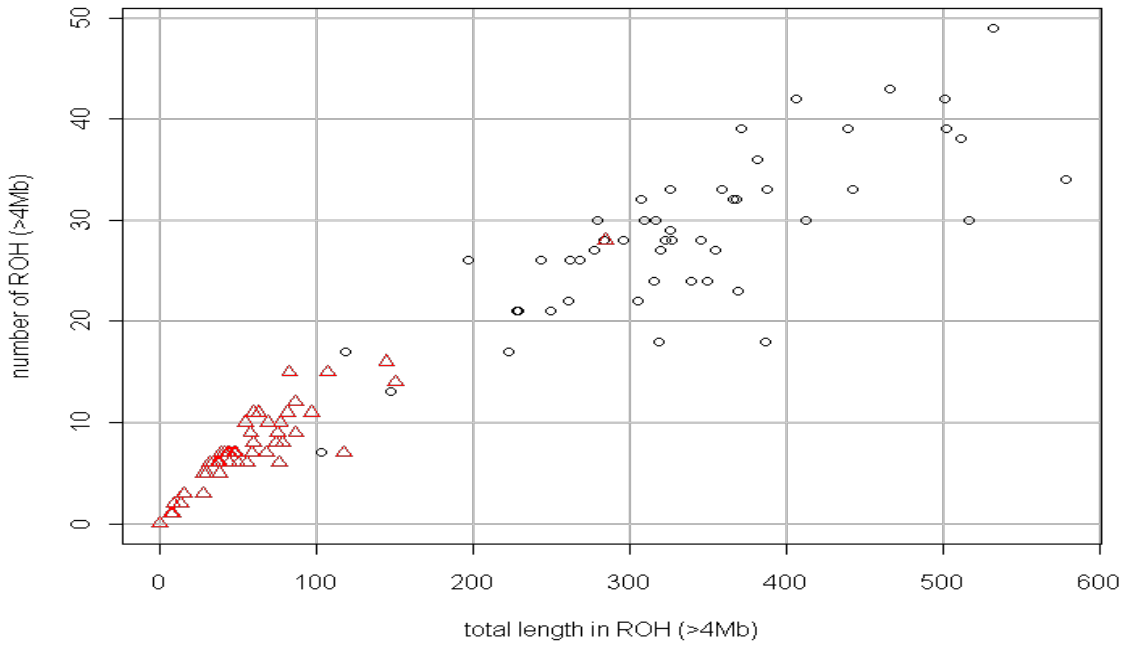

Figure 3 The ROH profile of animals with extreme values for F_{pedT}; red triangles: 50 animals with minimal F_{pedT}, black circles: 50 animals with maximum F_{pedT}

DISCUSSION

We analyzed animals from four cattle breeds with different inbreeding background in order to

derive levels of autozygosity based on ROH (F_{ROH}). Furthermore, we correlated F_{ped} and F_{ROH} values and obtained relatively high correlations which imply that F_{ROH} provides a solid indication of individual level of inbreeding. Additionally analyzing breeds ROH profiles we extract information regarding inbreeding history and evaluate it comparing with the present knowledge of their inbreeding past.

Average values for F_{pedT} varied between 0.014 for Fleckvieh up to 0.041 for Brown Swiss and a similar range of values was obtained for F_{ROH8} and F_{ROH16} among all four breeds (Table 2). This indicates that inbreeding estimated from pedigree data has recent origin. On the other hand, values for F_{ROH1}, F_{ROH2} and F_{ROH4} had higher values varying between 0.030 for Fleckvieh up to 0.142 for Brown Swiss (Table 2). According to this we state that F_{ped} is mainly explaining recent inbreeding while inbreeding coefficients based on ROH can capture inbreeding originating from far past if we take into account shorter ROH. Co-occurrence of ROH in regions with extended linkage disequilibrium (LD) and low recombination rates is reported in human studies of outbred populations (Gibson *et al.* 2006, Curtis *et al.* 2008). Due to this common extended haplotypes can partly contribute to high F_{ROH} estimates with shorter cut-off values. Additionally, substantial differences in defining criteria for ROH as well as differences in algorithms for detection of ROH can be taken into account as possible factors influencing F_{ROH} estimates.

Analyzing correlations between F_{ROH} and F_{ped} estimates we do not observe substantial differences (Table 4). However, correlations between pedigree inbreeding and F_{ROH4} and F_{ROH8} are slightly higher than for other F_{ROH} estimates (Table 4). No similar studies in animal genetics have been carried out for comparison. Still, human studies can provide some information. For instance, the correlation (r=0.86) calculated between measures based on proportion of ROH (>1.5Mb) in genome and pedigree inbreeding estimates from inhabitants of the Orkney Islands (McQuillan et al., 2008) was higher compared to our results in similar categories of ROH (F_{ROH1}, F_{ROH2}). The strongest correlations we obtained for F_{ROH1} were 0.714 for Brown Swiss while the lowest one for F_{ROH1} was

0.485 for Norwegian Red (Table 4). Lower correlations could be explained by poor pedigree estimation caused by errors in cattle pedigree records compared to the pedigree of the human population residing in a remote area.

In Figure 3, we notice that number and length of ROH increase with increase of pedigree inbreeding. In addition, we can easily distinguish animals with minimal and maximal inbreeding coefficients with regard to ROH pattern. Animals with minimal F_{pedT} estimates has small proportion of genome in ROH (<200Mb) along with the small number of ROH (Figure 3) except one outlier. On other side animals with maximal F_{pedT} estimates have a large proportion of genome in ROH along with increase of number of ROH with outliers. We assume that the outlier from the group with minimal F_{pedT} estimates is a consequence of pedigree errors while outliers from the group with maximal F_{pedT} estimates could potentially represent animals with inbreeding accumulated over a large number of generations.

F_{ROH} estimates confirmed the comparatively high level of inbreeding of the Brown Swiss bulls involved in the analysis. While most of these bulls are of Austrian origin, very large portions of their pedigrees trace back to the U.S. Brown Swiss population, with imports of semen starting in the early 1970ies (Sölkner et al., 1998). The U.S. Brown Swiss population is genetically small, mostly derived from 21 male and 169 female animals imported from 1869 to 1906 (Yoder and Lush, 1936). Unfortunately, information of large parts of the U.S. pedigrees tracing the ancestry further back was not available for analysis. The relatively high levels of pedigree inbreeding and of long ROH (Table 2, Figure 2) are due to the import of semen of a limited number of U.S. bulls and subsequent interbreeding. Considering runs of homozygosity of 1Mb or longer, the average level of autozygosity of this population is 0.142, much higher than the 0.042 based on the pedigree information available but consistent with the history of the breed derived from a small number of animals imported to the U.S. about 100 to 150 years ago.

Fleckvieh is a population with a large effective population size, partly due to the fact that breeding

work was until recently performed in independent regional associations (Sölkner et al., 1998). Using microsatellite markers Medugorac et al. (2009) found a large effective population size of 410 for this breed. This is consistent with the small proportion of autozygous genome and the relatively large number of short (1 – 2 Mb) segments.

Tyrol Grey is a local breed with small population size (<5000 registered cows). The breeding program involves a bull testing scheme with artificial insemination and natural mating. Sölkner et al. (1998) and subsequent analyses (unpublished) indicated substantially more inbreeding than for Fleckvieh for concurrent reference populations. The breed was also involved in the study of Medugorac et al. (2009), the effective population size was 200. ROH analyses confirm the result that the level of inbreeding is relatively low relative to the very small population size.

Norwegian Red is known by high heterogeneity which is result of historic admixture (Sodeland *et al*., 2011). In 2008, effective population size of Norwegian Red was 173 (Garmo R. T., 2009) and among the four breeds analyzed only Fleckvieh has larger effective population size (Sölkner *et al*. 1998). Maintaining of large effective population size is established through control of inbreeding and gene flow by importing sires from other Nordic countries. The ROH pattern of Norwegian Red indicates equal distribution of autozygosity between short segments (1 – 4 Mb) and long segments (> 4Mb) (Table 2). Additionally, Norwegian Red exhibit little variation in distribution of different length categories of ROH (Figure 2). Mean value of F_{pedT} for Norwegian Red population correspond the best with F_{ROH8} and F_{ROH16} estimates and it is in the same range as for Fleckvieh and Tyrol Grey.

In conclusion, levels of autozygosity derived from ROH provide a very good indication of individual inbreeding level particularly in case when pedigree data are not available. Additionally, levels of autozygosity derived from ROH provide more information about inbreeding to remote ancestors. Finally, applying the observational approach of ROH instead of the probabilistic approach of pedigree analysis most likely gives more precise information about individual levels of

autozygosity.

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