



ORIGINAL ARTICLE

Estimation of inbreeding and effective population size of full-blood wagyu cattle registered with the American Wagyu Cattle Association

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Keywords

Inbreeding coefficients; pedigree; runs of homozygosity.

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Received: 27 June 2013;

accepted: 7 November 2013

Summary

The objective of this research was to examine the population structure of full-blood (100%) Wagyu cattle registered in the United States with the American Wagyu Association, with the aim of estimating and comparing the levels of inbreeding from both pedigree and genotypic data. A total of 4132 full-blood Wagyu cattle pedigrees were assessed and used to compute the inbreeding coefficients (F_{IT} and F_{ST}) and the effective population size (N_e) from pedigree data for the period 1994 to 2011. In addition to pedigree analysis, 47 full-blood Wagyu cattle representing eight prominent sire lines in the American Wagyu cattle population were genotyped using the Illumina BovineSNP50 BeadChip. Genotypic data were then used to estimate genomic inbreeding coefficients (F_{ROH}) by calculating runs of homozygosity. The mean inbreeding coefficient based on the pedigree data was estimated at 4.80%. The effective population size averaged 17 between the years 1994 and 2011 with an increase of 42.9 in 2000 and a drop of 1.8 in 2011. Examination of the runs of homozygosity revealed that the 47 Wagyu cattle from the eight prominent sire lines had a mean genomic inbreeding coefficient (F_{ROH}) estimated at 9.08% compared to a mean inbreeding coefficient based on pedigree data of 4.8%. These data suggest that the mean genotype inbreeding coefficient of full-blood Wagyu cattle exceeds the inbreeding coefficient identified by pedigree. Inbreeding has increased slowly at a rate of 0.03% per year over the past 17 years. Wagyu breeders should continue to utilize many sires from divergent lines and consider outcrossing to other breeds to enhance genetic diversity and minimize the adverse effects of inbreeding in Wagyu.

Introduction

Wagyu is a breed of Japanese cattle whose origins can be traced back to the second century. The breed was originally developed for use as draft animals, and their inception coincided with the introduction of rice cultivation in Japan (Mannen *et al.* 1998). Their physicality and endurance made them ideal for the

cultivation of rice and transportation. In time, they became better known for their desirable meat characteristics, particularly their prominent intramuscular fat deposition (marbling) (Oyama 2011). For a brief period prior to 1944, Brown Swiss, Ayrshire, Simmental, Holstein, Korean and Angus cattle were imported and crossed with Wagyu cattle (Mukai *et al.* 1989).

The selection of sires within Wagyu was predominantly restricted to those sires residing within the same Japanese prefectures as the cows to which they were mated during most of the twentieth century (Nomura 1996). This changed with the implementation of genetic improvement programmes using BLUP methodology (Sasaki *et al.* 2006) and the use of artificial insemination. The use of these technologies led to the heavy use of a few prominent sires, and the offspring from five sires alone represented 42% of all registered animals (Nomura *et al.* 2001). The popularity of these sires reduced the genetic diversity within the Wagyu breed and resulted in a sharp increase in the rate of inbreeding and a drop in the inbreeding effective population size from 32 in 1986 to 14 in 1993 (Nomura *et al.* 2001). This was the result of the smaller number of sires used between 1991 and 1997 and the intensive use of a few sires facilitated by the use of artificial insemination.

The importation of the first Wagyu cattle into the United States began in 1973 with the shipment of four full-blood sires from Japan. The next importation of Wagyu cattle into the United States occurred in 1993 with two males and three females and represented the first exportation of Wagyu females from Japan. Additional importations from Japan to the United States followed: in 1994, eight males and 28 females were imported; in 1995, five males and 37 females; in 1997, nine males and 72 females; and in 1998, three males and 60 females were imported. The last importation of Wagyu animals into North America was in 1999 when one male and eight females were introduced into the United States. Most of the imported animals came from the Japanese prefectures of Tottori, Okayama and Hyogo.

The accumulation of inbreeding and the loss of genetic diversity is an issue of concern in the livestock industry. The last decade has witnessed a sharp incline in selection intensity, which contributes to increased inbreeding. Increases in inbreeding have also arisen as a result of the substantial progress and implementation of assisted reproductive technologies such as embryo transfer.

The objective of this study was to estimate and compare levels of inbreeding estimated using both pedigree and genotype data for full-blood Wagyu cattle registered with the American Wagyu Association and to assess the effective population size for the breed between 1994 to 2011. Establishing these parameters provides an opportunity to make informed selection and mating decisions with consideration of inbreeding levels and the maintenance of genetic diversity within the American Wagyu population.

Materials and methods

Inbreeding coefficient and effective population size from pedigree data

The pedigree records for 4132 full-blood Wagyu animals were obtained from the American Wagyu Association (Coeur d'Alene, Idaho). As no foreign germplasm has entered the breed since its establishment in Japan in 1944 (Nomura *et al.* 2001), a reliable estimate of the rate of inbreeding can be inferred in cattle with multiple generational pedigree data. Animals that were imported into the United States had pedigrees with fewer generations of ancestors identified (ancestors that remained in Japan were not necessarily identified) than Wagyu cattle that were the result of multigenerational matings in the United States.

The pedigree files for the 4132 full-blood Wagyu cattle were evaluated with the FSpeed Pro (Tenset Tech, Ltd., Cambridge, UK) breed management software program. Ten generations of pedigree data were searched to include all available ancestry and to obtain the overall mean inbreeding coefficients that resulted from the offspring born in that year (F_{IT}). The overall inbreeding coefficient of an individual, denoted F_{IT} , includes the contribution due to non-random mating within subpopulations (F_{IS}) and the contribution due to the subpopulation itself (F_{ST}), following the methods described by Wright (Wright 1950). In addition, the average number of generations that were full (number of generations where all pedigree records were complete) and the average depth of the furthest ancestor (number of generations to the most distant known ancestor) were also calculated. The effective population size was estimated from the increasing rate of F_{ST} for each year from a hypothetical population of random mating Wagyu where the population each year was derived from animals that produced registered offspring with the American Wagyu Association. The Wagyu inbreeding effective population size was estimated for each birth year from the rate of increase in F_{ST} per generation (Wright 1977; Caballero & Hill 1992). The annual increasing rate ($\Delta F_{ST,y}$) was calculated by:

$$\Delta F_{ST,y} = \frac{F_{ST,t} - F_{ST,t-1}}{1 - F_{ST,t-1}},$$

where $F_{ST,t-1}$ and $F_{ST,t}$ were the coefficients of F_{ST} in two successive years and y is year. The effective population size (N_e) of the Wagyu population was estimated as:

$$N_e = \frac{1}{2\Delta F_{ST,Y}L},$$

where L was the generation interval in years (Nomura *et al.* 2001).

The generation intervals were estimated based on four selection pathways [sire to breed son (L_{mm}), sire to breed daughter (L_{mf}), dam to breed son (L_{fm}) and dam to breed daughter (L_{ff})] based on the birth dates of registered animals in each year and the birth dates of their sires and dams. The average generation interval (L) was subsequently computed using the equation:

$$L = \frac{L_{mm} + L_{mf} + L_{fm} + L_{ff}}{4}.$$

Effective population size was also estimated by regressing by F_{IT} to determine whether the effective population was overestimated due to the presence of shallow pedigrees in some of the imported animals. Effective population was computed using the equation:

$$N_e = \frac{1}{2b},$$

where the slope (b) of the inbreeding coefficient was estimated from the mating of the parents that produced registered offspring that year.

Inbreeding coefficient estimation from genotypic data

Blood samples for 49 full-blood Wagyu animals representing eight prominent sire lines within the American Wagyu cattle population (Table 1) were obtained for DNA extraction. Blood samples were collected by a

Table 1 A Comparison of inbreeding coefficients estimated using pedigree or genotype data for eight full-blood Wagyu sires registered with the American Wagyu Association

| Sires | Registration number | Inbreeding coefficient based on pedigree (%) | Inbreeding coefficient based on genotype (%) |
|-------------------|---------------------|--|--|
| Kitaguni Junior | FB2422 | 0 | 1.66 |
| T.F. Itomichi ½ | FB2126 | 0 | 5.67 |
| T.F. Kikuhana | FB2127 | 18.7 | 6.37 |
| Kitateruyasudoi | FB0686 | 9.38 | 25.91 |
| Michifuku | FB1615 | 3.9 | 10.22 |
| Sanjirou | FB2501 | 9.3 | 16.17 |
| Takazakura | FB2892 | 0 | 0.99 |
| JVP Fukutsura 068 | FB2101 | 4.7 | 19.23 |
| Average | | 5.75 | 10.83 |

researcher and/or a practising veterinarian from the external jugular vein as approved by the Washington State University Animal Use Committee (#3608). DNA was extracted from each sample using the Pure-Gene DNA extraction kit (Qiagen, Valencia, CA, USA) according to the manufacturer's instructions. DNA concentration was measured using a Nanodrop 1000 spectrophotometer (Thermo Scientific, Wilmington, DE, USA), and purity was gauged by the spectrophotometer's 260/280 wavelength measurement. Samples with a 260/280 ratio of 1.8–2.0 were diluted to 50 ng/μl and genotyped at GeneSeek (Lincoln, NE, USA) using the Illumina (San Diego, CA, USA) BovineSNP50 BeadChip. This whole-genome single-nucleotide polymorphism (SNP) assay consisted of 54 609 SNPs with a mean and median spacing of 49.4 kb and 36.9 kb between SNPs, respectively.

Statistical analysis

Single-nucleotide polymorphisms were assessed for quality prior to inbreeding calculations using PLINK (Purcell *et al.* 2007). Single-nucleotide polymorphisms were removed if the minor allele frequency (MAF) was less than 5%, if the SNP failed to genotype in more than 10% of the samples or if the autosomal SNP failed the Hardy–Weinberg equilibrium test ($p < 0.001$). In addition, animals with a call rate of <95% were also removed.

After quality assurance filtering, genomic inbreeding coefficients (F_{ROH}) were estimated by calculating the runs of homozygosity (ROH) in each of the 49 genotyped samples. A ROH was defined as a specific number of consecutive SNPs that were all homozygous; by identifying blocks of SNPs, it was possible to determine SNPs that were inherited together, that is the proportion of SNPs identical by descent (IBD), allowing for an ascertainment of genomic inbreeding coefficients (F_{ROH}) (Bjelland *et al.* 2013). This is different from measuring inbreeding coefficients based on per cent homozygosity (F_{PH}), which examines each SNP independently for homozygosity, which makes it implausible to distinguish between SNPs identical by descent (IBD) and SNPs identical by state (IBS), preventing an accurate estimate of genomic inbreeding.

Runs of homozygosity were detected with PLINK with the following parameters: a sliding window of 50 SNP, a minimum ROH of 50 SNP with a minimum length of 1000(kb), 1 heterozygous SNP and 1 missing SNP were allowed within the sliding window (Howrigan *et al.* 2011). ROH identified were then used to calculate individual genomic inbreeding coefficients (F_{ROH}) incorporating the following formula:



Figure 1 Number of full-blood Wagyu registered with the American Wagyu Association by year of birth between 1994 and 2011.

$$F_{\text{ROH}} = \frac{\sum k \text{length}(\text{ROH}_k)}{L},$$

where K = number of ROH identified for each individual in kilobases and L = total length of the genome [2 612 820 kb (Zimin *et al.* 2009)]. Genomic inbreeding coefficients (F_{ROH}) were then compared to the inbreeding coefficients (F_{IT}) estimated from each of their 10 generation pedigrees.

Results

Total population size

Figure 1 shows the total population size of full-blood Wagyu calves born in the same year and registered with the American Wagyu association between 1994 and 2011. A total of 29 males and 207 females were imported from Japan into the United States, with the first 14 full-blood Wagyu animals being born in the United States in 1994. The Wagyu population, as measured by calves registered by birth year, steadily increased from 14 animals born in 1994 to a maximum of 698 animals born in 2009. Since 2009, the number of full-blood animals registered with the American Wagyu Association by birth year has declined, with a drop of 315 registered in 2011.

Pedigree inbreeding analysis

Figure 2 shows the mean annual pedigree estimated inbreeding coefficients (F_{IT}) by birth year. The mean inbreeding coefficient between 1994 and 2011 was estimated at $4.80 \pm 2.5\%$. The average number of

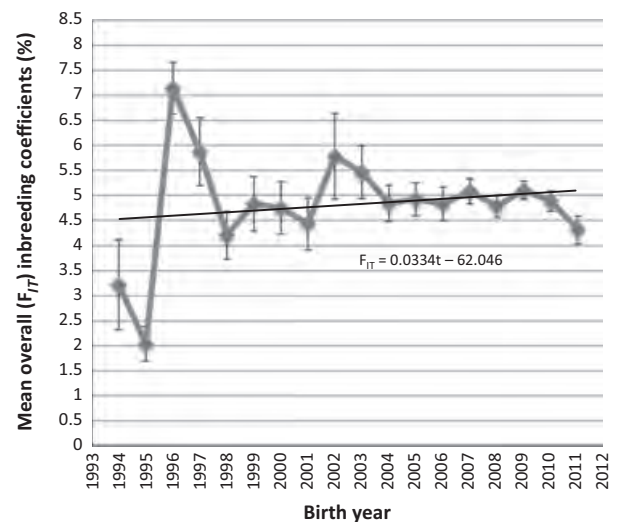


Figure 2 Arithmetic mean, standard errors and a fitted regression line for overall inbreeding coefficients (F_{IT}) estimated from pedigree records for full-blood Wagyu registered with the American Wagyu Association by year of birth between 1994 and 2011.

generations that were full (generations with complete identification of ancestors) and the average generation depth of the pedigree to the most distant ancestor was calculated as 3.37 and 8.14, respectively, for this period. In 1994, when the first full-blood Wagyu animals were born in the United States, the mean inbreeding coefficient was estimated at $3.2 \pm 0.9\%$. The mean inbreeding coefficient increased until 1996 when it reached a peak of $7.14 \pm 0.52\%$. The average inbreeding coefficient in 2011 was $4.3 \pm 0.27\%$. The largest inbreeding coefficient estimated for a single animal was 37.5% for an animal born in 2007.

Table 2 The average generation interval for full-blood wagyu registered with the American Wagyu Association

| Year | Generation interval (Years) |
|---------|-----------------------------|
| 1994 | 2.25 |
| 1995 | 3.32 |
| 1996 | 4.10 |
| 1997 | 4.50 |
| 1998 | 4.37 |
| 1999 | 4.12 |
| 2000 | 4.62 |
| 2001 | 5.10 |
| 2002 | 4.62 |
| 2003 | 4.97 |
| 2004 | 5.60 |
| 2005 | 5.90 |
| 2006 | 6.72 |
| 2007 | 7.00 |
| 2008 | 7.09 |
| 2009 | 6.11 |
| 2010 | 5.75 |
| 2011 | 6.40 |
| Average | 5.14 |

Generation intervals

Table 2 shows the generation intervals estimated as the average age of parents of full-blood progeny born and registered with the American Wagyu Association for each year from 1994 through 2011. The average generation interval over this period was 5.14 years with a low of 2.25 years in 1994 and a peak of 7.09 years in 2008, which is similar to observations made by McParland *et al.* (2007) for Charolais, Limousin, Hereford, Angus, Simmental and Holstein-Friesian cattle which had generation intervals of 6.17, 6.71, 6.03, 6.09, 6.54 and 6.66 years, respectively.

Effective population size

The effective population size estimate had an arithmetic mean of 17.0 ± 3.19 animals and a geometric mean of 13.2 ± 2.47 animals between 1994 and 2011, with an increase of 47.59 in 2002 and a drop of 2.3 in 1996. When comparing the total population size with the effective population size, 2009 shows the largest deviation with an effective population size of 11.6 animals compared to the full-blood American Wagyu Association registered population of 698 animals.

Effective population size was also estimated by regressing F_{IT} data. An effective population size of 14.97 animals was estimated using this method which is consistent with the geometric mean of 13.2 animals

estimated for effective population size described previously.

Inbreeding analysis from the BovineSNP50 Data

Single-nucleotide polymorphisms were evaluated for minor allele frequency, genotyping call rate and whether they were in Hardy–Weinberg equilibrium using PLINK (Purcell *et al.* 2007). Single-nucleotide polymorphisms with a minor allele frequency of less than 5% (20 443 SNPs) were removed from the analysis. An additional 1962 SNPs were removed due to a genotype failure rate of greater than 10% and 203 SNPs failed the Hardy–Weinberg equilibrium test ($p < 0.001$) and were removed. Two of the 49 genotyped individuals were removed for having a call rate $< 95\%$. After filtering, 33 167 SNPs were used to discover ROH.

The pedigree inbreeding coefficients (mean $F_{IT} = 4.8 \pm 0.25\%$) were lower than the mean genomic inbreeding coefficients for the 47 animals remaining after filtering (mean $F_{ROH} = 9.08 \pm 1.02\%$). Table 1 provides a summary of the pedigree estimated inbreeding coefficients (mean $F_{IT} = 5.75 \pm 2.36\%$) of each of eight prominent sires in the US Wagyu population compared with their genomic inbreeding coefficients (mean $F_{ROH} = 10.83 \pm 3.15\%$). These results are consistent with results reported by Decker *et al.* (2012) where the genomic data registered a higher rate of inbreeding than that found by pedigree analysis for registered Angus bulls. This suggests that the calculated values based on pedigree records may underestimate the true relatedness of the Wagyu cattle population. This disparity is likely observed from the fact that pedigree estimates of inbreeding assume that F_{IT} is set to zero for all animals at the base of the pedigree or as a result of pedigree errors and incomplete pedigree information.

Discussion

The genetic improvement of future generations is based upon recognizing the importance and achieving a balance between selection intensity and the maintenance of sufficient quantitative genetic variation within the population (Weigel & Lin 2000). The objective of this paper was to examine the population structure of registered American Wagyu cattle to identify and compare the rate of inbreeding using both pedigree and genomic data and to estimate the effective population size of Wagyu cattle in the United States. An accurate assessment of the levels of inbreeding and effective population size is important

to the future direction of breeding programmes, where the objective is to allow for the maintenance of genetic diversity in later generations while simultaneously generating genetic progress as response to selection.

The total population of full-blood Wagyu cattle registered in the American Wagyu Association increased from 14 individuals in 1994 to a maximum of 698 animals registered in 2009. While this demonstrates the growth of the Wagyu population, it is not a reflection of the genetic diversity within registered full-blood cattle, which is more accurately estimated by the effective population size. Effective population size is defined as the number of breeding individuals in an idealized population that would show the same amount of dispersion of allele frequencies under random genetic drift (Wright 1950). A population that undergoes a severe temporary reduction in size (bottleneck) or when a small group of animals within the population establishes a new population (founder effect), the effective population size is closer to the number of animals at the point of maximum contraction than the number of animals at its census maximum (Sjodin *et al.* 2005). Here, we estimated the effective population size for the full-blood Wagyu registered with the American Wagyu Association to average 17 animals between 1994 and 2011 with an increase of 47.59 animals in 2002 and a drop of 2.3 animals in 1996, indicating a low level of genetic diversity in the population. A number of researchers have argued that a minimum effective population size to enable the conservation of genetic diversity within endangered species should be set at 50 (Franklin 1980; Lande & Barrowclough 1987). This value was decreased to 40 by Goddard (1992). By balancing inbreeding depression against gain in fitness achieved through the process of natural selection, Meuwissen & Woolliams (1994) recommended a minimum effective population size of between 30 and 250 individuals. Estimates of the effective population size for Ayrshire, Brown Swiss, Guernsey, Holstein, Jersey and Angus breeds were 161, 61, 65, 39, 38 and 94 animals, respectively (Weigel & Lin 2002; Decker *et al.* 2012). Together this demonstrates that the current effective population size of registered full-blood Wagyu cattle is well below the threshold recommended.

The BovineSNP50 BeadChip, with 54 609 evenly spaced SNPs, provides a sufficient marker density to describe the co-ancestry between individuals, perhaps more so than pedigree data alone which suffers from pedigree errors and missing ancestors (Pryce *et al.* 2012). This was evident when the rates of inbreeding

estimated using pedigree and genotype data were compared. Inbreeding levels estimated from the SNP genotyping data were greater than when estimated from ten generation pedigree data, indicating that the inbreeding values estimated from pedigree data tend to underestimate homozygosity by descent among individuals. Pedigree data suffer from inaccuracies of assumed parentage unless confirmed by DNA typing. It has been estimated that 10% of offspring have incorrectly assigned paternity in registered animals (Sanders *et al.* 2006; Oliehoek & Bijma 2009). With the formation of the American Wagyu Association in 1993 came the requirement for DNA verification of parentage. Prior to this, it is likely that some of the pedigree information was inaccurate or incomplete. For example, Michifuku's pedigree was truncated at four generations because three great grand dams were unidentified in the pedigree. As a result, the pedigree inbreeding coefficient of 3.9% (Table 1) may have been underestimated. This is supported by the much larger F_{ROH} of 10.22 estimated for Michifuku. When ancestors are unidentified, such as in Michifuku's pedigree, the assumption is that the mean inbreeding coefficient of these animals is zero, similar to animals assigned to the base generation (who have neither parent identified). When this assumption is incorrect, the inbreeding coefficient based on pedigree is underestimated.

In addition, genomic inbreeding values may be overestimated due to the selection of SNPs in the genotyping assay. As the SNPs chosen to be placed on the Illumina genotyping platform were not based on sequence information of Wagyu cattle, it is possible that a greater proportion of SNPs in Wagyu are less polymorphic than in the breeds that were used to develop the Illumina assay. The effect of this bias would be an increase in observed homozygosity in some SNPs. Although the genomic inbreeding coefficients were measured by runs of homozygosity, rather than homozygosity at single SNPs, it is possible that the genomic inbreeding coefficients could be inflated due to this bias.

Six of the eight sires genotyped had pedigree inbreeding coefficients that were lower than the F_{ROH} . One notable exception was T.F. Kikuhana that had a much higher pedigree inbreeding coefficient than F_{ROH} . T.F. Kikuhana's pedigree shows that Dai-Nana Itozakura is prominent in its pedigree and accounts for its high pedigree inbreeding value. The reason for its low genotyping inbreeding coefficient is unknown. Confirmation of parentage by DNA genotyping has been required by the American Wagyu Association since its formation. However, there is always a

possibility that errors in pedigrees, or genotyping of T.F. Kikuhana or his parents (such as the mislabelling of a sample) could have occurred.

When an effective population size falls below a critical value, maintaining genetic diversity becomes the utmost importance. Emphasis on controlling the rate of increase of inbreeding within livestock species has received widespread attention. A recent study by Pryce and colleagues (Pryce *et al.* 2012) examined strategies for controlling inbreeding while maximizing genetic gain. The considered strategies examined the use of information from pedigree and genomic relationships and proposed using a genomic relationship matrix (GRM) rather than a pedigree relationship matrix (A) as an effective way to reduce levels of inbreeding while maximizing the rate of genetic improvement. Traditionally, mating strategies have managed inbreeding by the use of the A matrix (Kinghorn 2011). However, exchanging the A for the GRM provides a more precise estimate of the extent of relatedness among individuals, allowing a more effective reduction in the levels of inbreeding (VanRaden 2008; Hayes *et al.* 2009; Pryce *et al.* 2012).

The availability of high-density BovineSNP50 Bead-Chip data provides an opportunity to improve the accuracy of estimation of inbreeding coefficients to combat inbreeding depression in cattle. We have demonstrated that the full-blood Wagyu registered with the American Wagyu Association have reached a critically low effective population size and that for the Wagyu population to maintain genetic diversity, future breeding schemes may consider the registration of pure-blood animals for which 31/32 or 15/16 of their genome is Wagyu in origin to reduce inbreeding and increase the effective population size (N_e).

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