



Review

Genetic diversity, inbreeding and breeding practices in dogs: Results from pedigree analyses

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ABSTRACT

Pedigree analysis constitutes a classical approach for the study of the evolution of genetic diversity, genetic structure, history and breeding practices within a given breed. As a consequence of selection pressure, management in closed populations and historical bottlenecks, many dog breeds have experienced considerable inbreeding and show (on the basis of a pedigree approach) comparable diversity loss compared to other domestic species. This evolution is linked to breeding practices such as the overuse of popular sires or mating between related animals. The popular sire phenomenon is the most problematic breeding practice, since it has also led to the dissemination of a large number of inherited defects. The practice should be limited by taking measures such as restricting the number of litters (or offspring) per breeding animal.

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Introduction

Even though the word *pedigree*, which comes from the Old French term '*pié de grue*' (meaning foot of a crane) has been known and employed for centuries, its use on a population scale in dogs began to be developed only at the end of the 19th century with the creation of the first studbooks and kennel clubs. Since then, genealogical registries have proved to be crucial as selection and monitoring tools for breeding. Together with the breed standard, they also represent a key unifying element for breeders of a given breed.

Since a registry is intended to record all the information about known relationships within a given population, it also constitutes a useful source of data for the analysis of genetic diversity and structure of that population. Methods that measure this diversity (and more precisely average inbreeding coefficients) require computing time proportional to population size (Meuwissen and Luo, 1992). As a consequence, the first population studies on dogs were conducted only 20 years ago. Over the same time period, a large set of indicators has been developed for different purposes, such as computation of effective population size, analysis of genetic structure and detection of historical bottlenecks.

Such information is particularly useful in the canine species, where genetic bottlenecks, linked to breeding in closed populations, historical variations in population size and extensive use of popular sires, has had the effect of reducing the within-population

genetic diversity and increasing the incidence of inherited diseases (Mellersh, 2008).

An increasing number of studies has been conducted, either to characterise genetic structure, diversity and inbreeding of canine populations (Karjalainen and Ojala, 1997; Nielen et al., 2001; Cole et al., 2004; Lüpke and Distl, 2005; Leroy et al., 2006, 2009; Calboli et al., 2008; Głażewska, 2008; Oliehoek et al., 2009; Voges and Distl, 2009; Mäki, 2010), or to determine the prevalence of inherited defects (Ubbink et al., 1992, 1998, 1999, 2000; van der Beek et al., 1999; Mäki et al., 2001; Ólafsdóttir and Kristjánsson, 2008; Urfer, 2009; Wellmann and Pfeiffer, 2009; Lewis et al., 2010; Leroy and Baumung, 2011).

The aim of this article is to provide an overview of genealogical studies in dog breeds: (1) to recall the principles, specificities and possible limits of pedigree analyses; (2) on the basis of existing studies, to analyse the situation of dog breeds, with regard to their levels of genetic diversity, their population structure and their breeding practices, especially in relation to dissemination of inherited disorders and inbreeding depression; and (3) to provide recommendations for breeders and kennel clubs for management of diversity and control of inherited disorders.

Principles and specificities of genealogical analyses in the context of dog breeding

For a long time, pedigrees have been the only data source available for the monitoring of genetic diversity within a given population of dogs. Until the recent development of dense single nucleotide polymorphism chips, it was generally recommended to use pedigree information (when available) rather than

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molecular marker information for conservation purposes (Baumung and Sölkner, 2003; Fernandez et al., 2005). Based on Mendelian segregation rules, pedigree analysis can be used to follow gene transmission from generation to generation for an entire population. From this information, it is possible to infer the polymorphism of a given locus, neutral and without mutation, using the probability of either gene identity or gene origins.

However, pedigree analyses do have some limitations, mainly due to the limited extent of pedigree knowledge, i.e. the proportion of registered individuals in the history of the breed. This means, firstly, that these analyses are limited to a given number of generations, generally corresponding to the time when genealogies began to be registered by computers or, more rarely, to the beginning of genealogical registering within the breed. In the dog, most studies have been able to trace complete genealogies back to the 1960s or 1970s (Karjalainen and Ojala, 1997; Mäki et al., 2001; Nielen et al., 2001; Leroy et al., 2006, 2009; Calboli et al., 2008; Głazewska, 2008; Urfer, 2009; Mäki, 2010); some studies have been extended further back in time (Lüpke and Distl, 2005; Oliehoek et al., 2009; Wellmann and Pfeiffer, 2009), even to the late 19th Century (Voges and Distl, 2009).

Secondly, registrations of individuals with or without limited pedigree knowledge of the parents may also decrease the extent of overall known pedigree information and may introduce bias, since close relationships between some individuals may not be recognised. In some cases, these biases can be corrected by assigning 'orphans' to randomly chosen parents (Mucha and Windig, 2009), but if those individuals without known parents have very different origins (another country or another breed), this strategy may lead to other biases. For a given pedigree file, the extent of decrease in pedigree knowledge resulting from incomplete registration depends largely on whether or not the breed is distributed across several countries and whether the stud book is open or closed. Therefore, grouping pedigree files from different sources is a classical way to reduce the proportion of individuals without known parents.

Equivalent complete generations (EqG) constitutes the most common indicator to measure completeness of a given pedigree file. EqG is computed as the sum over all known ancestors of $1/2^t$, where t is the ancestor's generation number, which is equal to 1 for the parents, 2 for the grandparents and so on (Maignel et al., 1996). According to different breeds and studies (Mäki et al., 2001; Leroy et al., 2009; Oliehoek et al., 2009; Voges and Distl, 2009; Mäki, 2010), EqG shows a wide range of values, ranging from 0.3 in the Cursinu breed (a recently recognised breed; Leroy et al., 2009) to 13 in a study on the Nova Scotia duck tolling retriever (Mäki, 2010), where pedigree files were merged from 17 different countries, pedigrees going back to 1931.

A second limit of pedigree analysis is related to the possible existence of pedigree errors, resulting from registration errors, fraud or undetected matings (especially in dogs where multiple-paternity litters are possible). Pedigree errors may introduce bias in calculation of indicators such as inbreeding coefficient (Baumung and Sölkner, 2003). The average pedigree error rate has been reported to be around 10% in a range of livestock species (Oliehoek and Bijma, 2009). In dogs, the extent of pedigree errors appears to be less. In 2001, the American Kennel Club website reported a false paternity frequency of 4.4% among American dog breeds, while our own results indicate a pedigree error <10% (Leroy et al., 2011).

Measurement of genetic diversity in dog breeds

Several indicators have been used to assess genetic diversity on the basis of genealogical data, the most widely accepted being 'average inbreeding coefficient'. However, a given inbreeding level

measured within a population has to be interpreted with caution, since several meanings can be given to 'inbreeding', according to the way it is computed or the population studied. Inbreeding can be interpreted as a measure of shared ancestry, genetic drift or the system of mating (Templeton and Read, 1994).

In pedigree analysis, the coefficient of inbreeding F generally refers to 'identical by descent' (IBD) probability (Appendix A) for a given individual (Malécot, 1948). It is a measure of genetic diversity loss for individuals (not the population) and should not be interpolated at a population scale. When averaged over a population, F is not a measure of diversity loss and genetic drift, since it is also related to the genetic structure of the population, such as the existence of subpopulations or a specific mating system (Boichard et al., 1997).

It is possible to compute the diversity loss due to IBD through the 'average kinship coefficient' Φ , also called coancestry (Crow and Kimura, 1970). Kinship between two individuals is defined as the probability that two alleles (drawn at random, one from each individual) of a given locus are IBD, which would correspond to the degree of inbreeding of a potential offspring of both individuals. Averaged over a given population, Φ corresponds to the probability that two alleles randomly drawn are IBD, which makes the average Φ a better estimator of diversity loss at the population scale and explains why authors recommend minimising average kinship for conservation (Baumung and Sölkner, 2003). However, in canine studies, Φ is less frequently computed than average F ; calculation of average coancestry involves more computation time and several canine studies have focussed on the impact of individual F on traits linked to fitness.

In 14 studies across 106 dog breeds, average F and Φ values have a wide range (0–37%), with a median of ~4%. Three populations with average F values >25% (corresponding to matings between full sibs) are very small populations with deep pedigree knowledge (Cole et al., 2004; Głazewska, 2008; Mäki, 2010). However, breeds should not be compared directly on the basis of these IBD coefficients, since they are largely dependent on pedigree knowledge, which can be illustrated by the significant correlation ($r = 0.41$, $P < 0.001$) between F and EqG (on the basis of the 96 breeds for which an EqG was available or could be approximated).

Due to the relative nature of inbreeding (Kristensen and Sorensen, 2005), it is more common to use the inbreeding increase over time (also called generation ΔF or inbreeding rate), since the detrimental effect of inbreeding is due more to the rate at which inbreeding accumulates in the population (or the fact that inbreeding is 'old' or 'new') rather than inbreeding itself (Ballou, 1997).

ΔF can be computed by linear regression of F over time (Falconer and Mackay, 1996) or by using an approximate rooting of F by EqG (Gutiérrez et al., 2009). Instead of using the inbreeding rate directly, the following formula is frequently used to compute realised effective population size (N_e): $N_e = 1/2\Delta F$. N_e as well as being more or less corrected for pedigree knowledge (like ΔF), has the advantage of referring directly to a population size; it is also the usual measure for the assessment of risk status (Gandini et al., 2004).

Although it is difficult to link a given population size with a given risk, acceptable values of ΔF per generation should not be <0.5–1% (corresponding to N_e values of 50–100) to limit the extent of inbreeding depression (Bijma, 2000). On the basis of five studies in dogs, the median value of N_e across 66 breeds was ~93, with 13 breeds having N_e values <50, which is an issue of concern. These 13 breeds included local breeds with small population size, such as the Tyrolean hound (Voges and Distl, 2009) and the Braque Saint Germain (Leroy et al., 2009). They also included some breeds with large population sizes, such as Boxers in the UK, which were calculated to have an N_e of only 45 for a reference population of 44,500 over two generations, i.e. considered to be a small population from a genetic point of view (Calboli et al., 2008).

It should also be noted that (on the basis of a pedigree approach) dog breeds have, on average, comparable levels of genetic diversity to those of other domestic species. For instance, N_e ranges were 64–127 in cattle (McParland et al., 2007), 65–231 in French sheep breeds (Danchin-Burge et al., 2010) and 74–113 in US pig breeds (Welsh et al., 2010).

Genealogical analysis and information on breed history and breed structure

Investigations on the basis of pedigree files of the history of a breed (as far as the pedigree is known) or its genetic structure may allow subpopulations to be identified that make different contributions to genetic diversity. Pedigree analysis may also permit identification of the original carrier of a specific inherited defect. Population structure should be assessed before performing linkage association studies (Quignon et al., 2007).

Methods based on probabilities of gene origin constitute an alternative method to assess genetic diversity in animal populations. They are based on measures of the genetic contributions of founders, ancestors or founder genomes to the diversity of a population (estimated on the basis of their respective effective numbers f_e , f_a and f_g). These comparisons are useful for detecting possible genetic bottlenecks and effects of genetic drift within a given population (Boichard et al., 1997). Different studies using this approach in dog breeds (Cole et al., 2004; Leroy et al., 2006, 2009; Głażewska, 2008; Oliehoek et al., 2009; Voges and Distl, 2009; Mäki, 2010) have demonstrated a range of impacts due to bottlenecks (comparing f_a/f_e values) and genetic drift (comparing f_g/f_a values).

As an example, Voges and Distl (2009) demonstrated that early bottlenecks in Hannoverian hound breeds had a strong impact, with a large difference between f_e (42) and f_a (20). In contrast, in the Bavarian mountain hound breed, values for f_e (44) and f_a (34) were closer, indicating a more balanced use of animals for breeding through the history of the breed. However, in both breeds, drift seemed to reduce genetic diversity markedly, since the number of equivalent genomes was low both for Hannoverian hound breeds (6) and the Bavarian mountain hound breed (11). Values for f_a/f_e and f_g/f_a were in the range of 0.2–0.97 for Hannoverian hound breeds and 0.13–0.45 for the Bavarian mountain hound breed, reflecting the history, population size and pedigree knowledge of the different breeds.

Several parameters may have an impact on the genetic structure of a dog breed, including geographical distribution, existence of varieties within the breed (linked to some morphological traits), specific breeding rules and mating practices. These parameters may give rise to more or less genetically differentiated subpopulations within a breed, demonstrated by analysis of molecular diversity (Quignon et al., 2007; Björnerfeldt et al., 2008). The simple comparison of average Φ and F may constitute an indicator of breed structure, F averaged over a population also being influenced by the population structure and breeding practices.

Several approaches have been proposed for analysis of the population structure of given breeds on the basis of pedigree analysis, using indicators similar to molecular F -statistics (Calboli et al., 2008; Leroy and Baumung, 2011), analysis of kinship matrices by principal component analysis (Calboli et al., 2008) or hierarchical cluster approaches (Ubbink et al., 1998, 1999, 2000; Oliehoek et al., 2009; Wellmann and Pfeiffer, 2009). These studies have demonstrated variations in population structure according to breed (Calboli et al., 2008; Leroy et al., 2009; Leroy and Baumung, 2011). For instance, increased structure level can be found in breeds with closed varieties based on colour or size, for example in the English cocker spaniel and Poodle breeds (Leroy et al.,

2009). It can also be seen where mating occurs between close relatives, as in the Berger des Pyrénées breed (Leroy and Baumung, 2011). In the Iceland sheepdog, Oliehoek et al. (2009) showed that regular exchanges of genetic material could reduce the degree of differentiation between dogs in different countries, even though geographic distribution was not independent of the genetic structure of the breed.

Breeding practices, inbreeding and inherited disorders

Breeding and selection practices may have an impact on genetic structure of the breed. They also affect the evolution of genetic diversity within a given breed, as well as risks linked to the dissemination of genetic disorders. Some of those practices and their effects are linked to selection goals and breed standards (Higgins and Nicholas, 2008; Asher et al., 2009; Collins et al., 2011) but will not be considered further here since pedigree analyses mainly deal with loci that are not selected. However, the impact of some of these practices (e.g. extensive use of popular sires, choice of partners to be mated) on genetic diversity will be examined, followed by a discussion of their impact on the health of dogs.

Since the basis of artificial selection is that only a limited number of chosen animals are allowed to reproduce, it is logical to find that there is a large inequality in the use of breeding animals in domestic species. Some canine sires that are considered by breeders to be most fit for selection purposes may have more than 2500 offspring (Calboli et al., 2008). From the point of view of genetic diversity, the first consequence of this practice (the 'popular sire' effect) is a decrease in genetic diversity in proportion to the inequality in use of breeding animals, both at individual and population levels. As an illustration, in a simulated population in which the effective number of sires decreases from 267 (random mating) to 38 (10% of 400 potential sires making 100% of the matings), Leroy and Baumung (2011) showed that expected homozygosity (equivalent to average kinship) after 25 generations was multiplied by five.

Mating practices (i.e. which sire is mated with which dam) can also have an impact on genetic diversity. These practices can be divided into two categories depending on whether breeding animals are on average more ('line breeding' and 'close breeding') or less ('outbreeding' and 'outcrossing') related in comparison with random mating conditions. Line breeding and close breeding (which can be differentiated depending on the relationship level between breeding animals) are usually used to define practices that involve the intentional mating of related individuals, such as when breeders attempt to fix or maintain specific traits from a common ancestor. These practices have an impact on genetic diversity at the individual level (inbreeding), yet do not have by a substantial impact on diversity at the population level (kinship) (Leroy et al., 2009; Leroy and Baumung, 2011). Conversely, the main purpose of outbreeding and outcrossing is to introduce some variability within a given subpopulation or line, with the aim to increase genetic diversity at the individual level; at the breed level, outcrossing increases genetic diversity.

Evolution of genetic diversity at individual and population levels due to these practices may have different consequences on breed health. These consequences can be divided into two categories, according to whether the alleles involved have a substantial impact on breed health (i.e. with reference to inherited disorders) or are mildly deleterious (i.e. with reference to inbreeding depression) (Bataillon and Kirkpatrick, 2000).

Here, consideration will only be given to fully recessive alleles, since these are considered to be both the main mode of inheritance for inherited disorders in dogs (Patterson, 2000) and the main phenomenon involved in inbreeding depression (Charlesworth and

Charlesworth, 1999). The probability of fixation or loss of a given allele is related to the amount of genetic drift within the breed; given a large number of deleterious alleles within a population, the probability that some of these alleles will attain high frequency is increased in populations with a lower N_e (Crow and Kimura, 1970). Given the recessive nature of the deleterious allele, the incidence of the defect is also likely to be increased in populations with an over-representation of homozygous individuals (i.e. with reduced individual genetic diversity in comparison with population diversity).

However, over-representation of homozygous individuals may also have positive effects, since it has the effect of increasing the exposure of recessive alleles to selection (Urfer, 2009; Wellmann and Pfeiffer, 2009). This leads to: (1) increased inbreeding purge, since a larger number of deleterious alleles are likely to be removed by selection, with positive effects on traits linked to fitness, and (2) a more limited risk of dissemination of a specific defect, the purging rate being increased with a larger proportion of homozygous individuals. Purging rate is also related to the selective disadvantage of the deleterious alleles (Gulisija and Crow, 2007), which is a function both of fitness reduction and breeding policy within the breed.

Given that the breeding practices described above have various effects on genetic diversity at the individual and population levels, they also have different impacts on inbreeding depression, inbreeding purging, dissemination risks and incidence of inherited disorders (Table 1). The popular sire effect is likely to increase dissemination risk, inbreeding depression, inbreeding purging and the incidence of inherited disorders (Wellmann and Pfeiffer, 2009; Leroy and Baumung, 2011). In comparison, close breeding and line breeding should lead to increased inbreeding depression, inbreeding purging and disorder incidence, while disorder dissemination risks should be reduced. These effects occur faster under close breeding (Leroy and Baumung, 2011). In contrast, outbreeding and outcrossing should lead to a decreased incidence of defects and less inbreeding depression; on the other hand, they result in a decreased inbreeding purge and an increased risk of dissemination of defects, since carriers are more difficult to identify and remove (Wellmann and Pfeiffer, 2009).

It is not easy to quantify the impact of these practices, since they depend on the mating system, demographic history of the breed and the genetic mechanism involved (Ballou, 1997); of course the genetic mechanism is not always known, especially for inbreeding depression and purging (Wellmann and Pfeiffer, 2009). Several studies have analysed the impact of inbreeding depression on traits linked to reproduction or occurrence of specific diseases (Ubbink et al., 1992; van der Beek et al., 1999; Mäki et al., 2001; Ólafsdóttir and Kristjánsson, 2008; Urfer, 2009). In most of those studies, significant but limited effects of inbreeding depression were found, e.g. hip dysplasia in German shepherd dogs and Golden retrievers (Mäki et al., 2001) and fertil-

ity in Irish wolfhounds (Urfer, 2009). The effects of inbreeding purging in dogs have not been investigated. However, based on studies in other domestic species (Gulisija and Crow, 2007; McParland et al., 2009), only limited effects of purging are to be expected in dog breeds.

Finally, it has not been possible to assess the relationship between N_e and the occurrence of specific inherited defects in dogs. However, the intense selection pressure applied in closed populations of limited size (in addition to indirect selection associated with morphological breeding goals), obviously constitutes one of the main reasons why over 1000 inherited conditions have been reported in dogs (Mellersh, 2008). This highlights the necessity for breeding organisations and individual breeders to improve management of genetic diversity in dog breeds.

Recommendations

This review has assessed the level of genetic diversity within canine breeds and the impact on breed health. Decreases in genetic diversity in breeds of dogs do not appear to be any worse than in other domestic species. However, better management of the existing diversity should constitute an important concern for clubs and breeders. Different breeding methods have been developed to maintain genetic diversity within a breed, for instance optimising the contribution of the parents to minimise the average kinship (Fernandez et al., 2005). These methods may place constraints on breeders (i.e. limiting the choice of breeding animals to be mated) but can be recommended for breeds with problematic genetic diversity.

The popular sire phenomenon constitutes by far the most problematic breeding practice in terms of the reduction of diversity and risk of dissemination of inherited defects. A simple measure to limit deleterious popular sire effects can be to restrict the number of litters (or offspring) per breeding animal. Such a measure has already been applied in some breed clubs (Mäki, 2010) and the Fédération Cynologique Internationale (FCI) recently recommended that, within a breed, no dog should have more offspring than 5% of the number of puppies registered in the breed population over a 5-year period. Such measures may have positive effects on genetic diversity, especially if the choice of the threshold is made on a breed-by-breed basis, taking into account the population size, level of diversity and demographic history. To avoid substantial bottlenecks, the use of breeding animals from original/seldom-used lines should also be promoted by kennel clubs; identification of such lines is feasible on the basis of pedigree (or molecular) analysis.

Among other practices examined, mating of close relatives may have an impact on breed health, by increasing inbreeding depression and the occurrence of genetic disorders (for a given deleterious allele frequency). In theory, mating of close relatives also reduces the risks of dissemination of deleterious alleles and

Table 1
Theoretical impact of some breeding practices on genetic diversity and different parameters linked to health of dog breeds.

Breeding practice	Inequality in use of breeding animals	Mating practices			
		Close breeding	Line breeding	Outbreeding	Outcrossing
Genetic diversity	Population level Individual level	Decreased Decreased	No impact Decreased	No impact Decreased	Increased Increased
Inherited disorders (autosomal recessive)	Dissemination risks	Increased	Decreased	Increased	Increased
	Proportion of individuals expressing disorder	Increased	Increased	Decreased	Decreased
Inbreeding depression		Increased	Increased	Decreased	Decreased
Inbreeding purging		Increased	Increased	Decreased	Decreased

increases inbreeding purging. However, no evidence of inbreeding purge has ever been shown in dogs and thus further investigation is required. Furthermore, since there are animal welfare concerns regarding practices such as close breeding, they should not be recommended to breeders.

Outbreeding is a potentially useful tool, especially to introduce diversity or remove an inherited disease from a given line. However, outbreeding choices should be supported by exhaustive pedigree analyses to identify well differentiated subpopulations. Outcrossing is another potentially useful option, since it is the only way to introduce diversity to an established breed. The choice of the individual(s) to be used for introgression should be made by the club with regard to the history and selection goals in the breed. Moreover, special attention should be given to genetic disorders to avoid the introduction of specific inherited diseases to the breed through introgression.

Conclusions

Although better management of genetic diversity may reduce the risk of dissemination of new inherited disorders, priority should also be given to reducing the incidence of inherited diseases. Identification of an increasing number of genes implicated in inherited diseases, as well as implementation of efficient breeding policies, will permit such a goal to be reached. However, such a challenge will not be achieved without the full cooperation of veterinarians, owners and breeders.

Conflict of interest statement

The author of this paper has no financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

Appendix A

Glossary of terms

Close breeding: Mating between closely related individuals (e.g. full sibs).

Effective population size (Ne): The number of breeding individuals in a population under random selection and random mating that would show the same decrease of genetic diversity as the population studied.

Identical by descent (IBD): Two or more alleles that are identical copies of the same ancestral allele, i.e. inherited from a common ancestor.

Inbreeding depression: The deleterious effect of inbreeding on a given trait (commonly related to fitness), either due to increased expression of deleterious recessive alleles or to a reduced positive effect of over-dominance on the trait.

Inbreeding purging: Removal of deleterious alleles from a population under inbreeding and selection.

Line breeding: Mating between pairs more related than under random mating conditions.

Outbreeding: Mating between pairs less related than under random mating conditions.

Outcrossing: Mating using breeding animals from different breeds.

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