Breeding Strategies Against Genetic Disorders In Dog Breeds

G. Leroy[*†], M. Abitbol[‡]

Introduction

According to Mellersh (2008), over 1000 genetic defects have been reported in dogs, with a wide range of incidence depending on breeds and diseases (Brooks and Sargan, (2001)). Breeding against these inherited conditions becomes therefore a major concern for owners and breeders. However, despite an increasing number of gene tests available, breed clubs often do not know which strategy to adopt, especially concerning the use of interesting studs that may be disease carriers, and are unaware of the impact of such policies on genetic diversity. This study was designed to investigate the effects of various strategies that may be used against a specific disease, making use of simulations. Based on our results, we make suggestions to the breed clubs, which was rarely done in the past

Material and methods

Populations simulated. From a base population of 4000 individuals and with a sex ratio of 1:1, 20 discrete generations were simulated keeping the population constant. For each generation, two lists of dams and sires were supposed to represent the individuals considered by breeders as potential reproducers. Dams and sires were chosen within these two lists to produce 800 litters of 5 puppies each, according to the following rules:

- To represent the fact that, among other common practices, breeders frequently choose sires and dams sharing a common ancestor or origin (line breeding), 25% of the entire population was included in 10 lines, all lines being of equal size. Within each generation, a list of 10 potential sires and 20 potential dams was chosen randomly from each of the 10 lines, and the remaining potential 300 sires and 400 dams were chosen among individuals not belonging to lines, in order to end up with a total of 400 potential sires and 800 potential dams. Offspring belonged to the line of their parents. However, in order to simulate gene flows between lines and the rest of the population, within each generation, the line was changed randomly for 10% of the offspring.
- To analyse the effect of an imbalanced use of reproducers (the popular sire effect), a sub-sample of 40 “popular sires” was randomly picked from the list of 400 potential sires, including 10 sires belonging to the 10 lines respectively. Popular sires were randomly sampled within this sub-sample to perform 50% of the matings, other matings being performed by sires randomly chosen among the other sires. In order to take into account the fact that a popular sire is likely to be the offspring of another popular sire, a popular sire has given a 70 % chance of being offspring of another popular sire, sampling being random other while. Dams were chosen randomly within their lists.

[*] AgroParisTech, UMR 1313 Génétique Animale et Biologie Intégrative, F-75000 Paris, France
[†] INRA, UMR 1313 Génétique Animale et Biologie Intégrative, F-78000 Jouy-en-Josas, France
[‡] INRA, ENV Alfort, UMR955 Génétique Fonctionnelle et Médicale, F-94704 Maisons Alfort, France

Disease inheritance and breeding policies. Our simulation included a single gene with two alleles (*A* and *a*), homozygous individuals *aa* being regarded as affected by the genetic defect. We elected to set the initial frequency at 0.20,which corresponds for instance to that of the US Field Trial Labrador centronuclear myopathy and 0.50, which corresponds for instance to that of the American Staffordshire Terrier cerebellar ataxia (data from: www.antagene.com). In order to simulate the allele spread within the various lines, we considered that the defect could be identified only late in the life of animals and was therefore not counter-selected until generation 10. We then assumed that a genetic test had been developed and that every potential reproducer was tested. We then applied one of four following rules:
NA: no particular policy applied and no selection implemented against the disease.
P1: From generation 10 on, the only matings allowed were *AA*x*AA* and *AA*x*Aa*.
P2: In generation 10, the only matings allowed were *AA*x*AA* and *AA*x*Aa*. Then, from generation 11 on, the only matings allowed were *AA*x*AA*.
P3: From generation 10 on, the only matings allowed were *AA*x*AA*.
For a given generation, from lists of potential reproducers, sub-lists of homozygous healthy individuals and heterozygous individuals were made. Dams and then compatible Sires were chosen within the sub-list depending on the constraints chosen. When for a given generation, a sub-list was found empty within a given line, a new sub-list was then sampled among remaining potential reproducers outside the line. Offspring of those matings were however considered as belonging to the original line.

The simulations were carried out using Fortran 90. Evolution of allele frequencies and average kinship Φ were measured and averaged over 1000 iterations for each policy option and initial frequency. For more detailed information on the simulation methods, see Leroy and Baumung (2010).

Results and discussion

Parameters were chosen to resemble those found in some real breeds. As an example, when no particular breeding policy was applied, the effective numbers of sires and dams used per generation were of the same order in the simulation (403 and 108 respectively) as those in some breeds raised in France that have a similar population size like Shar Peï (448 and 134 respectively) or Griffon Korthals (428 and 102 respectively). Population structures (fixation indices) were also quite similar between simulated populations and those breeds (Leroy and Baumung (2010)).

When no particular breeding policy was applied, the average kinship increased linearly by 0.19% per generation, reaching values close to 4% at generation 20 (Figure 1). For instance, in the Shar Peï breed, Leroy et al. (2009) found an average kinship of 1.2% for 4.7 equivalent generations traced, which is in keeping with the results of our simulations. By contrast, in the Griffon Korthals breed, kinship reached 4.3% for 8.5 equivalent generations traced, while Φ was on average lower than the 2% after 9 generations in our simulation. This difference may be due to some bottleneck events that occurred in the early generations of that breed.

The effects of the breeding policies on the frequency of the deleterious allele were quite predictable. Since, in our model, we considered that the disease by itself had no effect on

reproduction, when no policy was applied, the *a* allele frequency did not evolve. When the *P1* policy was applied, allowing healthy carriers *Aa* to reproduce with homozygous healthy *AA* individuals, there was a decrease in the frequency of allele *a* which was proportional to its frequency. For instance, if according to Figure 1, the frequency of *a* dropped from 0.2 to 0.1 in 3 generations, it took then 7 further generations to reach 0.05. Of course, when eventually all the carriers of allele *a* were removed from reproduction (*P3* policy and *P2* policy after generation 11), the frequency dropped to 0 in a single generation.

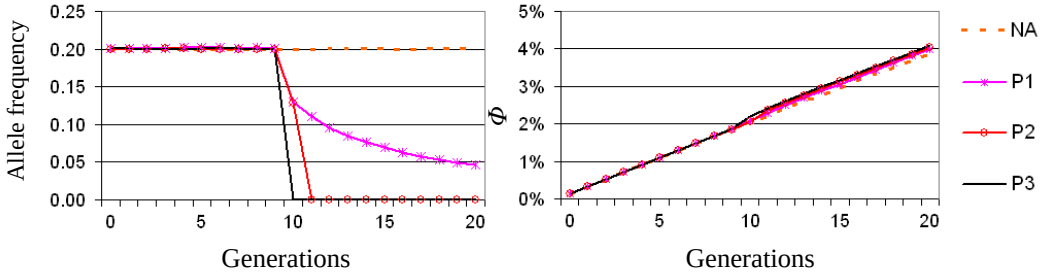

Figure 1: Evolution in the frequency of a deleterious allele and average kinship *Φ* under various mating policies, assuming an initial allele frequency of 0.20

Concerning evolution of genetic diversity, when the initial frequency of the deleterious allele amounted to 0.2, the impact on the increase in kinship was very limited, whatever the breeding policy used (Figure 1). On the contrary, when the initial frequency of *a* amounted to 0.5, there was a strong increase in kinship in the two generations following generation 10 (Figure 2). When comparing situations where no selection was made (*NA*), the average *Φ* increased by 0.6%, 0.7% and 1% under policies *P1*, *P2* and *P3* respectively.

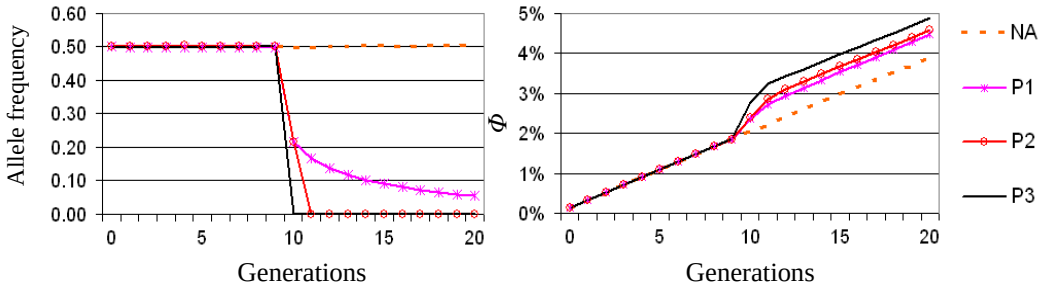

Figure 2: Evolution in the frequency of a deleterious allele and average kinship *Φ* under various mating policies, assuming an initial allele frequency of 0.50

When implementing a breeding program against a specific disease for which a genetic test is available, several points have to be considered such as the efficiency and the duration of the program, its potential impact on genetic diversity, and the decision to remove or not from reproduction carriers who might otherwise be interesting for selection. Here we considered several strategies, and their impact on these points.

The fastest way to get rid of any genetic disorder is clearly to bar from reproduction carriers and affected individuals (*P3*). Such a strategy has three major disadvantages. (1) If the

incidence of the disease is high (close to 0.5 or higher), it has a clear impact on genetic diversity, as illustrated in our study. (2) Applying such a policy would lead breeders to keep from using carriers that might be potential interesting studs. (3) In other respects, it may also have some political implications within the breed club if some breeders own mostly carriers.
Allowing healthy carriers to mate with non-carriers (*P1*) for an undetermined period seems also to be problematic, as this policy will only lead to a reduction in the incidence of the disease but not to its disappearance. Moreover, since at least reproducing offspring of the carriers should be tested for several generations, such a strategy is likely to be expensive for the breeders. However, among the active breeding policies proposed, *P1* seems to have the smallest impact on genetic diversity.
Policy *P2* represents a compromise between the two other strategies. It lets breeders mate healthy carriers with non-carriers for one generation (about 4 years in dogs), such carriers being barred from reproduction from then on. This gives breeders owning a lot of carriers a chance to purge their kennel without completely losing their lines. If the incidence is very high, the impact of such a policy on genetic diversity seems also to be quite comparable to that of the *P1* strategy, as illustrated in Figure 2.

Conclusion

To conclude, choices should be made by clubs depending on the incidence of the disease concerned and on the political context. When the allele frequency is below 20%, some strong policy (*P3*) may be introduced. The impact on genetic diversity will remain limited. If the frequency is substantially higher than 20 %, a delay could eventually be given for breeders to use carriers (*P2)*, up to 4 years, depending of the situation. If the frequency reaches value quite larger that 20%, *P2* policy should be preferred in order to limit decrease of genetic diversity within the breed. Using such an approach, the disease linked to the test should be eradicated. As a consequence, systematic testing of reproducers may be stopped, theoretically after one or two generations, depending on the strategy chosen. However, since breeds are rarely strictly closed populations, it may be important to still test individuals imported or registered without parents known, even after the completion of the program.

Such considerations only apply once a disease has been identified and once an appropriate test has been developed. Thanks to the current progress in genomics, it is becoming easier and less costly to identify genes implicated in the transmission of genetic disorders. In order to identify diseases with increasing incidence, and because breeding strategies are easier to implement with limited consequences, while the incidence is still low, frequent surveys within the breed would also be advisable, in order to detect genetic defects as early as possible.

References

Brooks, M., and Sargan, D.R. (2001) In: *The genetics of the dog*, pages 191–265.

Leroy, G., Verrier, E., Meriaux, J.C. *et al.* (2009). *Anim. Genet.*, 40: 323–332.

Leroy, G., and Baumung, R. (2010). *Anim. Genet.*, *In Press*

Mellersh, C. (2008) *Vet. J.*, 178:46–52.