

## Letter of support

The long joint history of dogs and humans has provided us with the wonderful cultural heritage of a wide variety of dog breeds. However, breeding populations based on relatively small founder populations in closed studbooks increases the risk of inbreeding depression, a phenomenon which has been well studied and documented in wild, captive, and domestic populations (e.g. Keller & Waller 2002, Boakes et al. 2007, Leroy 2014). Inbreeding depression arises mainly when recessive deleterious alleles negatively affect fitness-related traits such as lifespan due to increased levels of homozygosity (Charlesworth & Willis 2009). Today we know that some of the breeding practices used by breeders of purebred dogs have unintentionally led to an increased burden of inherited disease in many breeds (e.g. Summers et al. 2010). Founder effects, bottlenecks, genetic drift, as well as some breeding strategies such as the overuse of popular sires or excluding too many dogs from breeding (e.g. carriers of testable recessive disease-linked mutations) all contribute to the decline in genetic diversity/increased level of inbreeding observed in many modern dog breeds (e.g. Yordy et al. 2020, Bannash et al. 2021).

The benefits of increased genetic diversity or a low level of inbreeding have been well documented in dogs. One measure of genetic diversity that is often used in research is average genome-wide heterozygosity. It is negatively correlated with the average coefficient of inbreeding across breeds (Yordy et al. 2020, Bannash et al. 2021). Less inbred / more genetically diverse breeds carry on average a lower burden of morbidity and live longer than more inbred / less diverse breeds (Bannash et al. 2021, Kraus et al. 2023). Similarly, analyses with several breeds suggest that less inbred individuals have lower juvenile mortality (Leroy et al 2015), live longer on average (Armstrong 2000, Yordy et al. 2020, Wade et al. 2023) and have larger litters (Leroy et al 2015, Chu et al. 2019). These observations are consistent with findings from genetic health testing. Increased genetic diversity has recently been shown to be correlated with a lower number of recessive disease-linked mutations in both mixed breed and purebred dogs (Donner et al. 2023).

At this time, Miniature American Shepherds and Miniature Australian Shepherds are still genetically the same population (<https://embarkvet.com/resources/dog-breeds/miniature-american-shepherd/>). The breed currently has good levels of genetic diversity (median genome-wide heterozygosity of MAS is 41.2% compared to 36.0% for all purebreds and 44.9% for mixed breed dogs, Donner et al. 2023). Consistently, MAS currently still have a relatively low average genetic coefficient of inbreeding compared to many other breeds (Fig. 1). Still, recently, a breed-specific degenerative neurological disease has been described in the MAS (Progressive Neurological dystrophy – link), suggesting that mutations associated with this disease might have been enriched in the population due to a founder effect. Increased levels of inbreeding could lead to an increased prevalence of this disease and other yet unknown diseases present in the population.



The subpopulation of MAS currently registered with the AKC consists of a limited number of family groups which themselves show a high level of ancestor loss (Fig. 2). The closure of the AKC MAS subpopulation in the near future carries the danger of creating a bottleneck. As a consequence, the current genetic diversity of the breed could be reduced substantially. Even if this founder population would represent the genetic diversity of the MAS population at large, restricting it to a smaller size renders it more vulnerable to diversity-reducing processes such as genetic drift. Hence, the closure of the studbook would increase the risk of further breed-specific disease predispositions emerging and other detrimental effects on health and lifespan.

The fact that the overall MAS population with all its registry-specific subpopulations is large and still quite genetically diverse provides a unique opportunity to prevent what has happened in many other established breeds – a substantial loss of genetic diversity and concomitantly an increased risk of inherited disease. Studies in conservation biology show that having some gene-flow among subpopulations is important for maintaining genetic diversity (e.g. Frankham 2006, Reed 2004). This in turn allows more selection for desirable traits including breed type and selection against inherited diseases. As an additional benefit, the genetic management of this breed could be used as a model to track the outcome of relative health against similarly structured breeds with closed registries.

**In sum, allowing controlled on-going registration of dogs from other MAS registries as proposed by MASCUSA would facilitate the sustainable management of genetic diversity and invest in the future health of the breed. We therefore fully support this initiative to not close the AKC MAS studbook in the near future.**

Sincerely,

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## References

Armstrong: <https://www.dogenes.com/poodle/lifespan.html>

Bannasch D, Famula T, Donner J, Anderson H, Honkanen L, Batchner K, et al. The effect of inbreeding, body size and morphology on health in dog breeds. *Canine Med Genet.* 2021;8(1):12.

Boakes EH, Wang J, Amos W. An investigation of inbreeding depression and purging in captive pedigreed populations. *Heredity (Edinb).* 2007 Mar;98(3):172-82.

Charlesworth D, Willis JH. The genetics of inbreeding depression. *Nat Rev Genet.* 2009 Nov;10(11):783-96.

Chu ET, Simpson MJ, Diehl K, Page RL, Sams AJ, Boyko AR. Inbreeding depression causes reduced fecundity in Golden Retrievers. *Mamm Genome.* 2019 Jun;30(5-6):166-172.

Donner, Jonas, et al. Frequency and distribution of 152 genetic disease variants in over 100,000 mixed breed and purebred dogs." *PLoS genetics* 14.4 (2018): e1007361.

Frankham, R. Genetics and landscape connectivity. In Crooks, K., & Sanjayan, M. (Eds.). 2006. *Connectivity Conservation (Conservation Biology)*. Cambridge: Cambridge University Press.

Keller, L. F., & Waller, D. M. (2002). Inbreeding effects in wild populations. *Trends in ecology & evolution*, 17(5), 230-241.

Kraus C, Snyder-Mackler N, Promislow DEL. How size and genetic diversity shape lifespan across breeds of purebred dogs. *Geroscience.* 2023;45(2):627–43.

Leroy G. Inbreeding depression in livestock species: review and meta-analysis. *Anim Genet.* 2014 Oct;45(5):618-28.

Leroy G, Phocas F, Hedan B, Verrier E, Rognon X. Inbreeding impact on litter size and survival in selected canine breeds. *Vet J.* 2015 Jan;203(1):74-8.

Reed, D. (2004). Extinction risk in fragmented habitats. *Animal Conservation Forum*, 7(2), 181-191.

Summers JF, Diesel G, Asher L, McGreevy PD, Collins LM. Inherited defects in pedigree dogs. Part 2: Disorders that are not related to breed standards. *Vet J.* 2010 Jan;183(1):39-45.

Wade CM, Nuttall R, Liu S. Comprehensive analysis of geographic and breed-purpose influences on genetic diversity and inherited disease risk in the Doberman dog breed. *Canine Med Genet.* 2023 Jun 5;10(1):7.

Yordy J, Kraus C, Hayward JJ, White ME, Shannon LM, Creevy KE, et al. Body size, inbreeding, and lifespan in domestic dogs. *Conserv Genet.* 2020;21(1):137–48.