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Effects of Long Term Selection in the Border Collie Dog Breed: Inbreeding Purge of Canine Hip and Elbow Dysplasia

Virág Ács¹, György Kövér², János Farkas², Árpád Bokor³, István Nagy⁴

¹Department of Animal Nutrition, Kaposvár University, Kaposvár, H-7400, 40, Guba S. str., Hungary;

²Department of Mathematics and Informatics, Kaposvár University, Kaposvár, H-7400, 40, Guba S. str., Hungary;

³Department of Hippology, Kaposvár University, Kaposvár, H-7400, 40, Guba S. str., Hungary;

⁴Department of Animal Science, Kaposvár University, Kaposvár, H-7400, 40, Guba S. str., Hungary;

*Corresponding author: acs.virag@ke.hu

Simple Summary: For dog breeders, health is one of the main criteria when choosing a breeding animal, thus selection for good anatomy is the key to reduce orthopedic disorders. In many dog breeds, radiographic screening for canine hip and elbow dysplasia is a compulsory test for breeding, however, these multifactorial traits are determined by genetic and environmental factors. Therefore, it is really hard to eliminate these disorders from the population. In natural selection, such traits can “purge” out of the with inbreeding. The study aimed to examine the inbreeding-purge of canine hip and elbow dysplasia in the border collie breed. The main conclusion was, that with over-representation of homozygous individuals may have a positive effect on hip and elbow conformation.

Abstract: Pedigree data of 13 339 border collie dog was collected along with hip and elbow dysplasia records (1352 CHD and 524 CED), and an inbreeding-purging (IP) model was created to detect possible purging. Ancestral inbreeding coefficients were calculated by gene dropping simulation method (Ballou, 1997; Kalinowski, 2000) with GRain 2.0 (Baumung et al., 2015) software. GLMM models were created to the examined traits fitted with a log-link Poisson distribution, added to the estimated values of classical inbreeding coefficient (F_w), and the ancestral inbreeding (F_{BAL} , F_{KAL} , F_{KAL_NEW}) as covariates. The effective population size decreased in the examined period along with the increase of F_w however, slight differences were found as a consequence of breeding dog imports. CHD values were getting lower by the expansion of F_{BAL} as the alleles were inbred in the past. For CHD signs of purging were obtained. There was a positive trend regarding the breeding activity (both sire and dam of the future litters should be screened and certified free from CHD and CED), as years of selection increased the frequency of alleles with favorable hip and elbow conformation. Division of the ancestral inbreeding coefficient shows that alleles IBD for the first time (F_{KAL_NEW}) had a negative effect on both traits, while F_{KAL} shows favorable results for alleles IBD in the past generations. Some authors had proven this phenomenon in captive populations or experimental conditions however, no evidence of inbreeding purge has ever been described in dog populations. Despite the various breeding practices, it seems, that alleles of these polygenic disorders could be successfully purged out of the population with long term selection.

Keywords: Border Collie, inbreeding, purging, hip dysplasia, elbow dysplasia

1. Introduction

Dog breeds had passed several morphological and functional changes during centuries as a result of selective breeding. In the 19th century- at the time of Kennel Club foundations- dog populations went through the greatest bottleneck effect in dog breeding history. With the rising interest of purebred dogs, selection pressure affected dog breeds considerably, they suffered a higher loss of genetic diversity than other domesticated species (Leroy, 2011). Calboli et al., (2008) also reported, that >90% of unique genetic variants are lost in only 6 generations of selective breeding. Due to the repeated use of popular sires, breeding for phenotype and linebreeding also resulted in a smaller effective population size (Leroy and Baumung, 2011). While undesirable traits are eliminated from other agricultural species as breeding programs focus on production and longevity, selection in dog breeding concentrates on looking and behaving in certain ways (Mellersh, 2008). Alongside the transformation of breed functions (from working dogs to companion pets) lower within breed heterogeneity and unhealthy anatomy led to inherited disorders which can be connected to breed standards highlighting show ring appearance. Some of these health problems are monogenic, (produced by a single gene or allele) on the other hand, there are multifactorial traits influenced by genetic factors and the environment.

The border collie was mainly a working breed during the last two centuries however, nowadays show-line dogs make a great part of the population as a good family pet with lower energy levels. Dog breeders and the different kennel clubs operate with compulsory genetic and clinic health tests for breeding animals (in Hungary, compulsory tests are only in the working line) to increase the chance to produce healthy offspring. The most common clinic tests for orthopedic disorders are screening of possible canine hip dysplasia (CHD) and elbow dysplasia (CED). These multifactorial traits are both affected by genetic and environmental components showing great incidence variability among breeds with mixed results of phenotypic selection (Malm et al., 2008; Lewis et al., 2010).

CHD affected dogs diagnosed by radiographic imaging have abnormal hip development with femoral head luxation and ossification delay (Peterson, 2017). Selection is based on phenotype by scaling images from normal to severe (Ginja et al., 2009). CED was previously defined as a combination of orthopedic disorders of the foreleg, such as fragmented medial coronoid process, osteochondritis, an incongruity of the elbow joint, and ununited anconeal process (Hazenwinkel, 2008). As a result, dysplasia categorized as severe or moderate is painful and frequently causes lameness.

Breeding schemes showed a diverse degree of improvement in hip and elbow joint confirmation due to different sample sizes assessment protocols (Lewis et al., 2010; Hou et al., 2013) and variation in the effectiveness of selection. CHD was registered to OFA (Orthopedic Foundation of Animals) in the '60s, to provide data for breeding programs by integrating genetic and phenotypic information of animals and support selection decisions (Kaneene et al., 1997; 2009). Heritability of CHD ranges between 0.46-0.75 (Oberbauer et al., 2017) while CED heritability varies between 0.01 to 0.36 (Baers et al., 2019), depending on the pedigree completeness and breed differences. In closed populations, such as purebred dog populations selection pressure and inbreeding may reduce fitness as inbreeding enhances the number of homozygotes of a certain allele (inbreeding depression). In conservation genetics, Frankham et al. (2014) proposed, that N_e should be at least 100 to avoid short-term inbreeding depression, this fact should be also used in dog breeding. Nevertheless, inbreeding promotes to express recessive alleles, it also gives a rise to the effectiveness of natural selection known as genetic "purge" (Kalinowski et al., 2000). Mutations can contribute to inbreeding depression, however many generations of selection may purge out the deleterious alleles, and leave the mildly deleterious ones to remain. In a real population, the detection of an inbreeding-purging concept is difficult, regarding the need for a complete pedigree.

The study aimed to examine the border collie breed in an inbreeding-purging concept for the canine hip and elbow dysplasia.

2. Materials and Methods

2.1 Data collection

The database of the examined population contained 13,339 individuals (5649 males and 7750 females) built up from electronic herd books and pedigrees from Hungarian breeders. Genealogy information was tracked back from the late 1800s to the present day. Records were created with EquiHun Pedigree Builder (Bokor, 2004) with the following parameters:

- Individual identity number
- Male parent
- Female parent
- Date of birth
- Country of birth (i.e. country of origin)

Pedigree analysis was previously described in detail by Ács et al., (2019) ancestral inbreeding coefficients were calculated by gene dropping simulation method (Ballou, 1997; Kalinowski, 2002) with GRain 2.0 (Baumung et al., 2015) to avoid overestimation of ancestral inbreeding. In the present study, 1 000 000 simulations were used, and correlations between all inbreeding coefficients were tested. 1352 CHD and 524 CED data were added to pedigrees for further evaluation. General requirements of hip- and elbow dysplasia screening were described in detail by FCI (Federation Cynologique Internationale), where the main regulations are:

- The minimum age of the dog for radiographic imaging is 1 year
- The dog must be identified by a microchip
- All dogs should be sufficiently sedated or anesthetized during the procedure to relax all muscles

The categories of CHD data were summarized in Table 1. For further evaluation, FCI categories were coded with numbers from 0 (excellent) to 4 (severe).

Table 1. Categories and code numbers of canine hip dysplasia

Hip rating	Category name	
A	Excellent	0
B	Good	1
C	Fair/Borderline	2
D	Mild	3
E	Severe	4

CED categories are described in Table 2. and coded from 0 (normal) to 3 (severe)

Table 2. Elbow rating categories

Elbow rating	Category
0	Normal: No sign of arthrosis
1	Slight: Osteophytes, less than 2 mm
2	Medium: Osteophytes from 2 to 5 mm
3	Severe: Osteophytes, more than 5 mm

2.2 Data analysis

R package 'lme4' was used (Bates et al., 2015), to make generalized linear mixed models (GLMM). Data were fitted with a log-link Poisson distribution. The models contained the following inbreeding coefficients as fixed effects:

- F_w : Inbreeding coefficient described by Wright (1922)
- F_{BAL} : Ancestral inbreeding coefficient, determined as the cumulative proportion of the genome exposed to inbreeding effects (Ballou, 1997). F_{BAL} was created to test the magnitude and effectiveness of inbreeding depression as the extent to which individual's ancestors have been subjected to inbreeding.
- F_{KAL} : Inbreeding coefficient defined by Kalinowski, (2000). The probability of alleles that had been autozygous (IBD) in the previous generations at least once, where the common ancestor is presented on both sides of the pedigree.
- F_{KAL_NEW} : Kalinowski new inbreeding coefficient, described as alleles IBD were inbred for the first time (Kalinowski, 2000)

The structure of the applied models are described in Table 3. as follows:

Table 3. Structure and fitting of the applied models

Model	Component models	AIC	
		ED	HD
1	$F_w + F_{BAL}$	105.08	2277.5
2	$F_{KAL} + F_{KAL_NEW}$	95.98	2279.5

F_w : inbreeding coefficient of the population; F_{BAL} : Ancestral inbreeding coefficient of the population; F_{KAL} : Kalinowski inbreeding coefficient of the population; F_{KAL_NEW} : Kalinowski "new" inbreeding coefficient of the population

The inbreeding coefficients were summarized by birth year, from the first date of radiographic examination. Effect plots of the applied models were created with the "effects" package in R (Fox and Weisberg, 2019) to display differences between the models and illustrate the IP.

To avoid the overestimation of ancestral inbreeding a stochastic approach was applied by gene dropping (Suwanlee et al., 2007) with GRain 2.0 (Baumung et al., 2015) due to the fact, that F_w and F_{BAL} are dependent. So, the procedure included two unique alleles assigned to each founder and generated the genotypes of all offspring along with the pedigree by Mendelian segregation rules.

3. Results

The effective population size of the border collie breed in the examined period (from the first litter born in Hungary until the present day) is demonstrated in Figure 1.

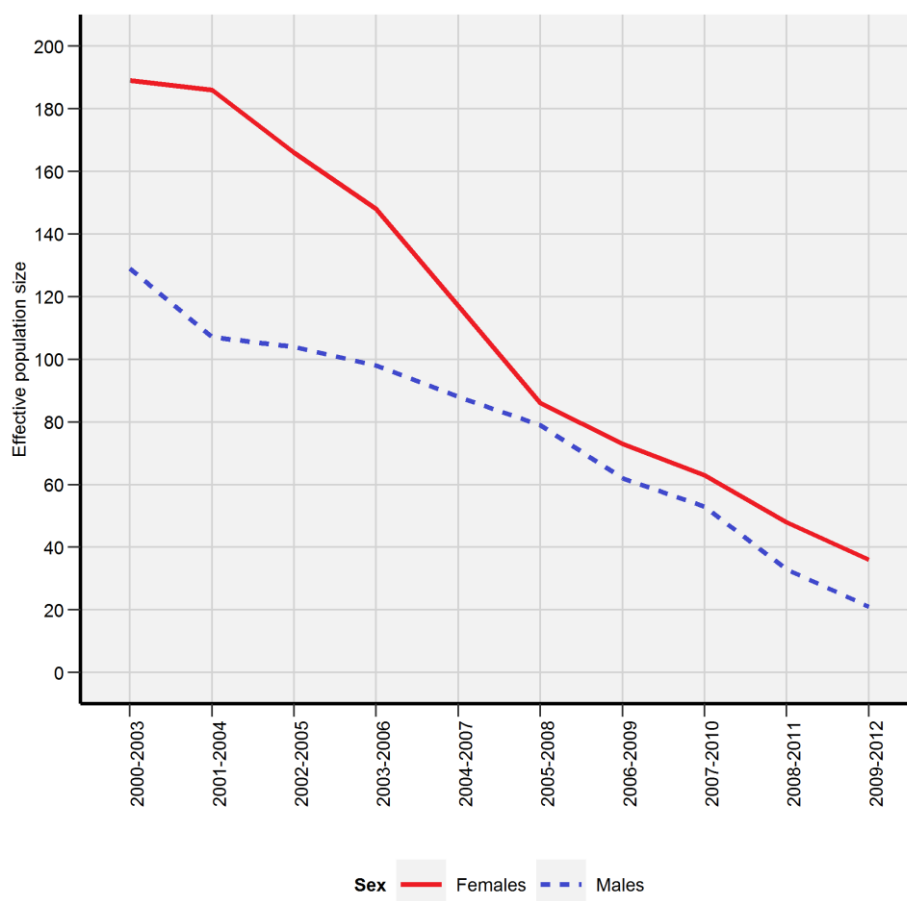


Figure 1. Effective population size of the border collie breed

The effective size of both male and female dogs decreased each year. Despite the popularity of the breed, owners usually buy cheaper dogs from unregistered breeders and the number of dogs with registered pedigree diminishes each year. Besides, using favored males for matings is a common trend in dog breeding which can lower the population size and enhance inbreeding. On the contrary, it can increase litter homogeneity which is highly preferred of the breeder's point of view.

Figure 2. summarizes the estimated values for the ancestral inbreeding coefficients and F_w by birth year.

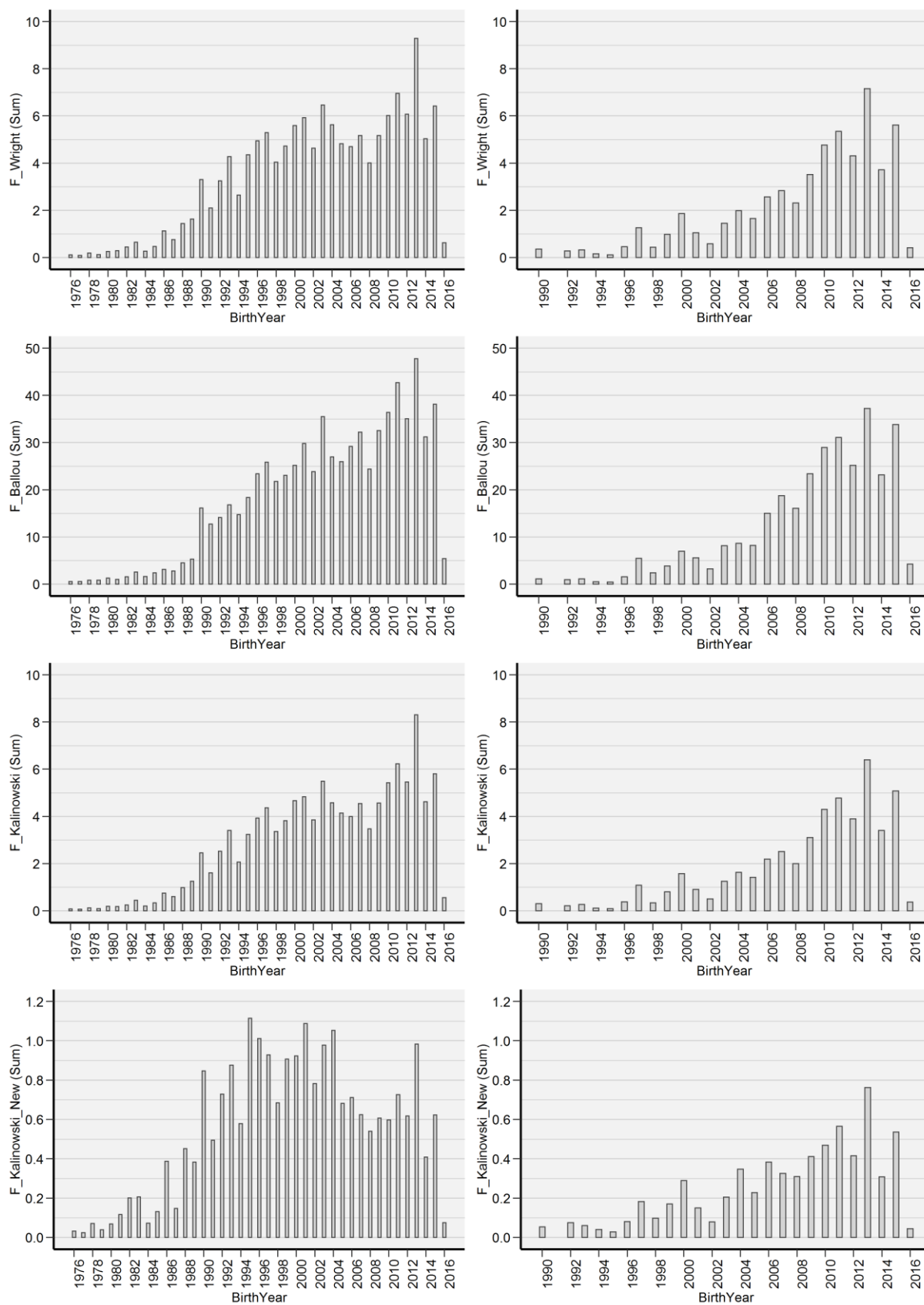


Figure 2. Sum of the estimated ancestral inbreeding coefficients by birth year

The sum of the estimated values for F_w increased year by year, however, differences were found between the examined years, as a consequence of breeding dog imports. From 2015 FCI collecting style

herding events became more popular in Europe, thus several breeding dogs from ISDS (International Sheep Dog Society) lines were imported to the country from Ireland and the UK. Looking at the estimated values for F_{BAL} coefficients, similar tendencies were observed. The first border collie arrived in Hungary in 1995, thus ancestral inbreeding enhanced as the first kennels started their breeding programs. For the applied models, averaged parameter estimates are summarised in Table 4.

Table 4. Averaged parameter estimates for the applied linear models

Model	1	2
	ED	HD
Variables		
F_W	0.10±0.05	0.10±0.05
F_{BAL}	0.60±0.08	0.54±0.11
F_{KAL}	0.09±0.44	0.08±0.04
F_{KAL_NEW}	0.01±0.01	0.01±0.01

Correlation coefficients of F_W and F_{BAL} were relatively weak (0.48), while it was strong (0.90) between F_{KAL} and F_W because of the part-whole relationship between them. Similar results were previously reported by McParland et al., (2009) examining the IP concept in the Irish Holstein-Friesian population.

3.1 Results for purging in canine hip dysplasia

Figure 3. demonstrates the effect plots of the inbreeding-purging concept of variables for CHD and visualizes F_W , F_{BAL} , F_{KAL} and F_{KAL_NEW} showing their effect on the examined trait.

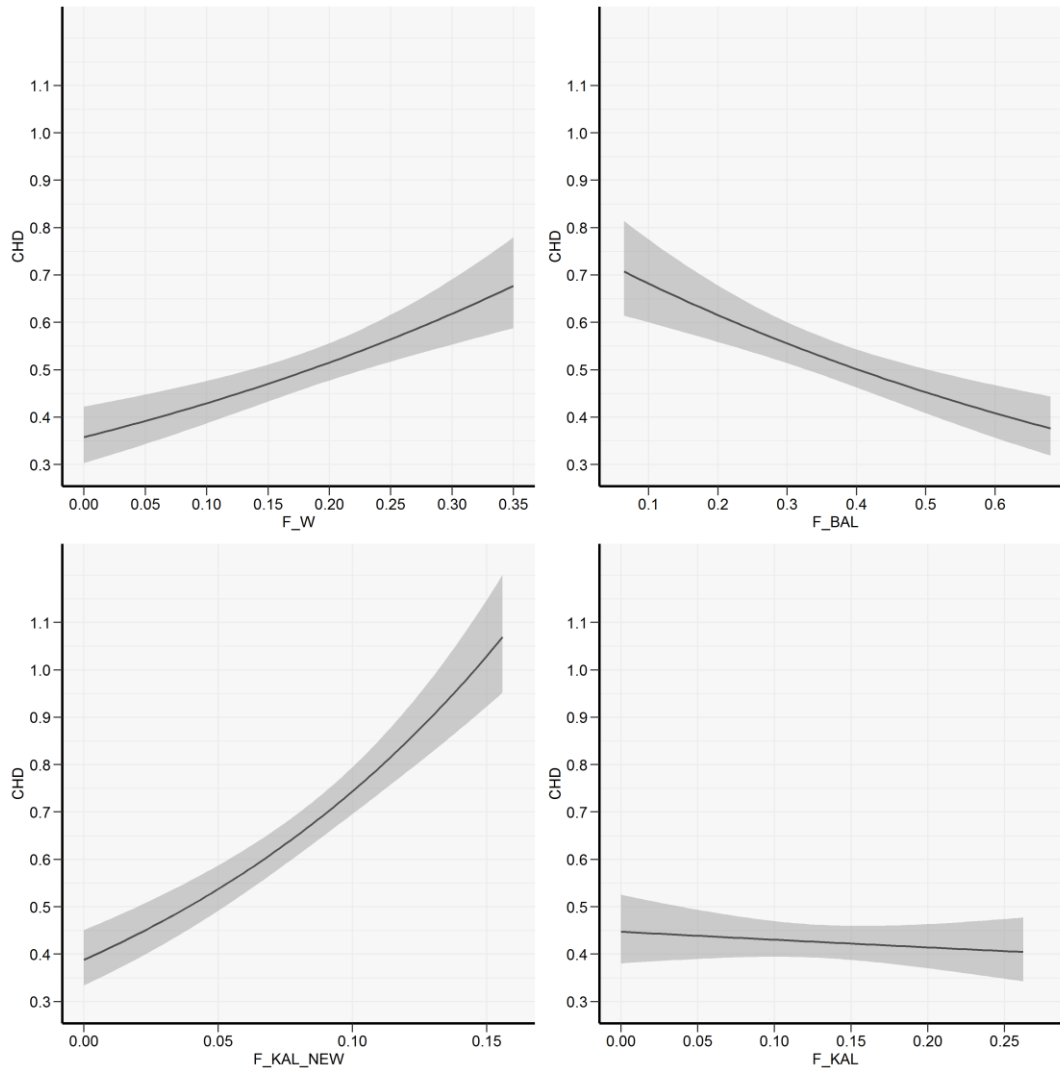


Figure 3. Effect plots of the models for CHD

The shaded area represents a pointwise confidence band for the fitted values, based on standard errors computed from the covariance matrix of the fitted coefficients. The rug plot in the bottom shows the location of values of inbreeding. In the case of F_W results, it is visible as the inbreeding coefficient increases year-by-year in the population a negative relationship between F_W and CHD is experienced and shows that the genetic load of partially deleterious alleles is still represented in the population. It can be seen that CHD values were getting lower by increasing F_{BAL} where alleles were inbred in the past. This may be the result of long-term selection for healthy hip results as a favorable trait.

Inbreeding coefficients for the best conformation values of CHD (score = 0) varied between 0.05 and 0.15. From 2000, good and excellent CHD results decreased, regarding F_W .

Looking at the ancestral inbreeding coefficient defined by Ballou, it is detectable that after an initial drop, the examined inbred population recovered its level of health, thus with the occurrence of purging through several generations, it should contain fewer deleterious alleles. The inbreeding coefficients defined by Kalinowski et al. (2000) were divided into two components (one part of the alleles were inbred in the past (F_{KAL}), and one part of alleles met at the first time (F_{KAL_NEW})).

Comparing the inbreeding coefficients by Kalinowski et al. (2000) it can be concluded, as the number alleles IBD in the past increased, the hip conformation results started to improve. Prior to the availability of phenotypic assessments, there was no possibility to pre-select breeding dogs by their

anatomical values. On the other hand, alleles IBD for the first time tends to have a negative effect on health. F_{KAL_NEW} , tend to be higher, the number of dogs with excellent and good hip results enhanced.

3.2 Results of purging in canine elbow dysplasia

Looking at the CED results of the border collie breed, similar results were found however, the estimated values of classical inbreeding coefficient and the ancestral inbreeding defined by Ballou (1997) do not show any significant differences ($p=0.32$). The effect plot for classical inbreeding and ancestral inbreeding is manifested in Figure 4.

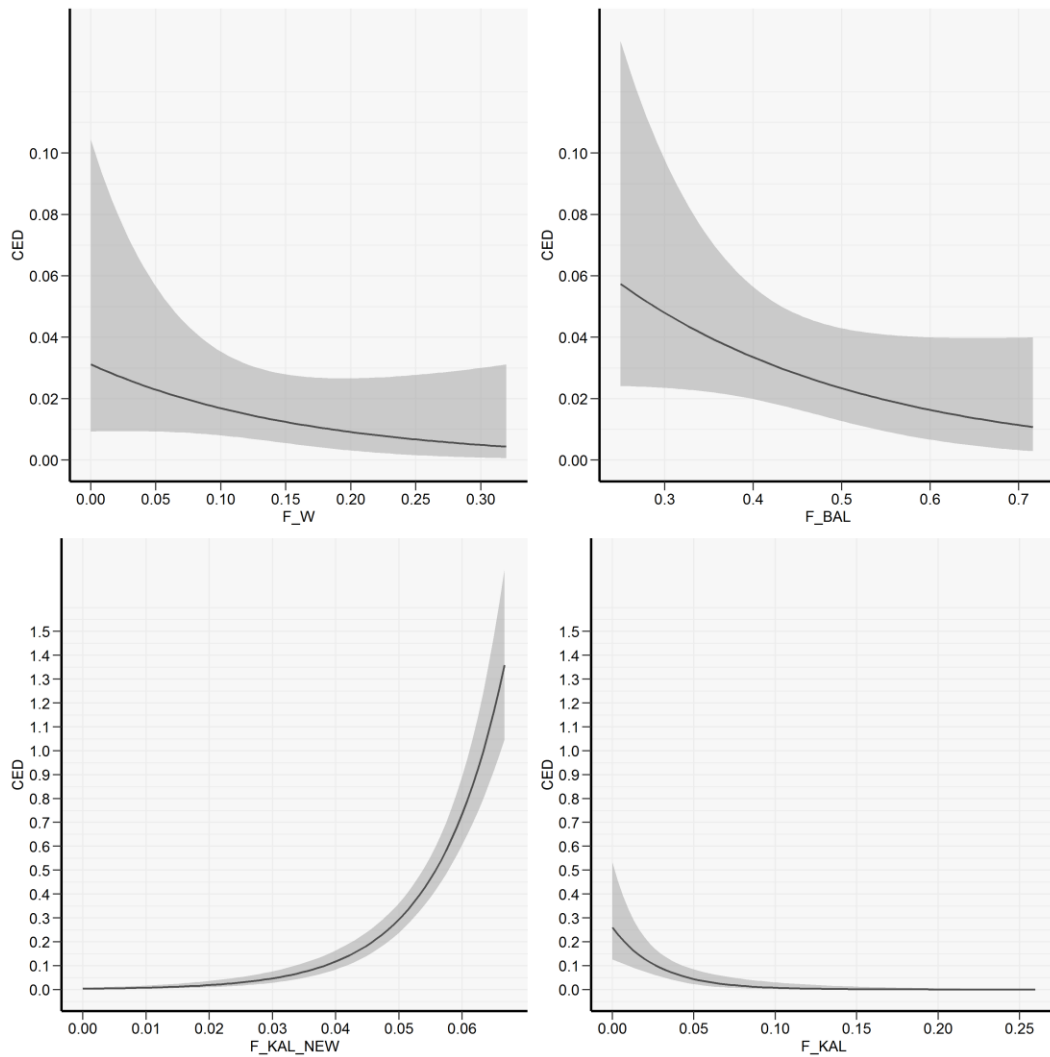


Figure 4. Effect plots of the models for CED

CED for selection criteria is very recent (radiographic imaging to detect this disorder started in the mid-2000s in Hungary), and still optional. It can be concluded, as the amount of the estimated classical inbreeding coefficient and the ancestral inbreeding rise, CED results improve. For F_{W} , the purging is partial. This result is also favorable however, only 2 out of these 524 scanned dogs had severe CED. After the division of the inbreeding coefficient into two parts, F_{KAL} and F_{KAL_NEW} for CED shows, that selective breeding was successful. On the other hand, this result demonstrates the differences between Ballou's and Kalinowski's concept. In this case, examining the estimated values for purging requires not just the classical inbreeding-purging concept, but the previously described ancestral inbreeding approaches.

4. Discussion

Within breed variation was previously described by Irion et al., (2003) and Leroy (2011), showing that dog populations had a great selection pressure and several bottlenecks. Overuse of popular sires and a large amount of unequally used breeding animals (Calboli et al., 2008) decrease genetic diversity. Nevertheless, other mating trends such as "outbreeding" and "outcrossing" may have a positive effect on genetic diversity and inbreeding depression (Leroy and Baumung, 2011). Thus, consequences in connection with the health status of the breed can be divided into two categories: alleles concerning lethal and sub-lethal mutations and mildly deleterious mutations that are only partially recessive (Bataillon and Kirkpatrick, 2000). The over-represented homozygous individuals might have a positive effect, since recessive alleles can purge out of the population (Urfer, 2009; Wellmann and Pfeiffer, 2009) by the increased amount of inbreeding and selection, having a positive effect on traits in connection with health. Our results show that the genetic trend for favorable hip and elbow conformation increased however, the genetic load was not completely excluded from the population.

The phenotypic trend for CHD and CED in 60 different dog breeds showed substantial differences according to Oberbauer et al., (2017). The study pointed, that out of the examined breeds, border collies are not in the group of breeds that are highly affected by orthopedic disorders. According to Hazewinkel et al., (2002) correlation between radiographic and physical signs depends on physical demands (working dogs and family pets are different due to muscularity), age, and the breed. Todd et al. (2018) previously reported a positive effect of selective breeding for exercise physiology and selective sweeps linked to genes influencing muscle fiber formation in thoroughbred horses. Keller et al., (1993), de la Riva et al., (2013) and Hart et al. (2014, 2016) also found that age at the X-ray examination has a serious impact on hip and elbow results.

The most often cases for purging are slow inbreeding and competitive conditions (López-Cortegano et al., 2016; Bersabé and García-Dorado, 2013). As our models proved, recessive deleterious alleles seemed to be purged in inbred ancestors, thus dogs with higher F_{BAL} and F_{KAL} , for both traits are expected to carry less of these alleles to the next generation, than individuals with the same level of inbreeding but lower ancestral inbreeding values. Boakes et al. (2007) previously described this phenomenon in captive populations.

5. Conclusions

Since definite purposes such as show and sport require different anatomical structures, the importance of these lines is outstanding, however, the contrasts of the selection of these dogs may increase the genetic distance. In the long run, continuous selection for different scopes such as show and work may disrupt the breed. The decreasing tendency of the effective population size points out a trend, that dog owners do not prefer to buy from registered breeders. In Hungary, the working line is at the greatest risk, regarding the number of breeding animals and the number of litters. However, this line represents the look and the original function of the breed. To maintain variability, the genetic contribution of some preferred males could be limited by mating schemes to help the breeders. Import

breeding dogs could be also a solution to this problem, on the other hand, breeding standards are slightly different between countries, so this needs collaboration between breeding organizations and scientists to improve the health of the next generation over looks.

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References

1. Ács, V.; Bokor, Á.; Nagy I. Population structure analysis of the border collie dog breed in Hungary. *Animals*, **2019**, *9*, 250.
2. Asher, L.; Diesel, G.; Summers, J.F.; McGreevy, P.D.; Collins, L.M. Inherited defects in pedigree dogs. Part 1: Disorders related to breed standards. *Vet. J.* **2009**, *182*, 402–11.
3. Baers, B.; Keller, G.G.; Famula, T.R.; Oberbauer, A. Heritability of Unilateral elbow dysplasia in the dog: A retrospective study of sire and dam influence. *Front. Vet. Sci.*, **2019**, *6*, 422.
4. Ballou, J.D. Ancestral inbreeding only minimally affects inbreeding depression in mammalian populations. *J. Hered.* **1997**, *88*, 169–178.
5. Baumung, R.; Farkas, J.; Boichard, D.; Mészáros, G.; Sölkner, J.; Curik, I. GRAIN: a computer program to calculate ancestral and partial inbreeding coefficients using gene dropping approach. *J. Anim. Breed. Genet.* **2015**, *132*, 100-108.
6. Bates, D.; Machler, M.; Bolker, B.; Walker, S. Fitting Linear Mixed-Effects Models Using lme4. *J. Stat. Soft.* **2015**, *67*, 1-48.
7. Bataillon, T.M.; Kirkpatrick, M. Inbreeding depression due to mildly deleterious mutations in finite populations: Size does matter. *Genet. Res.* **2000**, *75*, 75-81.
8. Bersabé, D.; García-Dorado, A. On the genetic parameter determining the efficiency of purging: an estimate for *Drosophila* egg to-pupae viability. *J. Evolution. Biol.* **2013**, *26*, 375–385.
9. Boakes, E.H.; Wang, J.; Amos, W. An investigation of inbreeding depression and purging in captive pedigreed populations. *J. Hered.* **2007**, *98*, 172–182.
10. Bokor, Á. Equihun Pedigree Builder –MS Access application specifically developed for genealogy records process. *Unpublished*, **2004**.
11. Calboli, F.C.F.; Sampson, J.; Fretwell, N.; Balding, D.J. Population structure and inbreeding from pedigree analysis of purebred dogs. *J. Genet.* **2008**, *179*, 593–601.
12. García-Dorado, A. Understanding and predicting the fitness decline of shrunk populations: inbreeding, purging, mutation, and standard selection. *J. Genet.* **2012**, *190*, 1461–1476.
13. García-Dorado, A.; Wang, J. López-Cortegano, L. Predictive model and software for inbreeding-purging analysis of pedigreed populations. *G3*. **2016**, *6*, 3593-3601.
14. Ginja, M.M.D.; Silvestre, A.M.; Honzolo-Orden, J.M.; Ferreira, A.J.A. Diagnosis, genetic control, and preventative management of canine hip dysplasia: a review. *Vet. J.* **2010**, *184*, 269–276.
15. Hart, B.L.; Hart, L.A.; Thigpen, A.P.; Willits, N.H. Long-term health effects of neutering dogs: comparison of labrador retrievers with golden retrievers. *PLOS ONE*, **2014**, *9*, e102241
16. Hart, B.L.; Hart, L.A.; Thigpen, A.P.; Willits, N.H. Neutering of German Shepherd Dogs: associated joint disorders, cancers, and urinary incontinence. *Vet. Med. Sci.* **2016**, *2*, 191–199.

17. Hazewinkel, H.; Nap, R. Elbow dysplasia, definition, and known aetiologies. *22nd annual meeting of the International Elbow Working Group*; München, **2007**
18. Hazewinkel, H. Screening for elbow dysplasia, grading according to IEWG. *33rd annual meeting IEWG Singapore, September 24th*. **2018**.
19. Hou, Y.; Wang, Y.; Lu, X.; Zhang, X.; Zhao, Q.; Todhunter R.J.; Zhang, Z. Monitoring hip and elbow dysplasia achieved modest genetic improvement of 74 dog breeds over 40 years in the USA. *PLoS One*, **2013**, 8, e76390.
20. FCI workshop on hip dysplasia, Dortmund, **1991**
21. Fox, J.; Weisberg, S. An R Companion to Applied Regression, 3rd edition. Sage, Thousand Oaks CA. <http://tinyurl.com/carbook>. **2019**.
22. Frankham, R.; Bradshaw, C.J.A.; Brook B.W. Genetics in conservation management: Revised recommendations for the 50/500 rules, Red List criteria, and population viability analyses". *Biol. Cons.* **2014**, 170, 56–63.
23. Irion, D.N.; Schaffer, A.L.; Famula, T.R.; Eggleston, M.L.; Hughes, S.S.; Pedersen, N.C. Analysis of Genetic Variation in 28 Dog Breed Populations With 100 Microsatellite Markers. *J. Hered.* **2003**, 94, 81–87.
24. Kalinowski, S.T.; Hedrick, P.V.; Miller, P.S. Inbreeding depression in the Speke's gazelle captive breeding program. *Cons. Biolog.* **2000**, 14, 1375–1384.
25. Kaneene, J.B.; Mostosky, U.V. Padgett, G.A. A retrospective cohort study of changes in hip joint phenotype of dogs in the United States. *J. Am. Vet. Med. Ass.* **1997**, 211, 1542-1544.
26. Kaneene, J.B.; Mostosky, U.V.; Miller, R. Update of a retrospective cohort study of changes in hip joint phenotype of dogs evaluated by the OFA in the United States, 1989-2003. *Vet. Surg.* **2009**, 38, 398-405.
27. Keller, G.; Bouchard, G.; Fagin, B.; Lattimer, J.; Ellersieck, M. Influence of the estrous cycle on coxofemoral joint subluxations. *Can. Pract.* **1993**.
28. Leroy, G. Genetic diversity, inbreeding, and breeding practices in dogs: Results from pedigree analyses. *Veterinary Journal*, **2011**, 189, 177–182.
29. Leroy, G.; Baumung, R. Mating practices and the dissemination of genetic disorders in domestic animals, based on the example of dog breeding. *Anim. Genet.* **2011**, 42, 66–74.
30. Lewis, T.W.; Woolliams, J.A.; Blott, S.C. Genetic evaluation of the nine component features of hip score in UK labrador retrievers. *PLOS ONE*. **2010**, 5(10):e13610.
31. López-Cortegano, E.; Vilas, A.; Caballero, A.; García-Dorado, A. Estimation of genetic purging under competitive conditions. *Evolution*, **2016**, 70, 1856–1870.
32. Malm, S.; Fikse, W.F.; Danell, B.; Strandberg, E. Genetic variation and genetic trends in hip and elbow dysplasia in Swedish Rottweiler and Bernese mountain dog. *J. Anim. Breed. Genet.* **2008**, 125, 403-412.
33. Marsden, C.D.; Ortega Del-Vecchyo D.; O'Brien D.P.; Taylor J.F; Ramirez O.; Vilá C.; Marques-Bonet T.; Schnabel R.D.; Wayne R.K; Lohmueller K.E. Bottlenecks and selective sweeps during domestication have increased deleterious genetic variation in dogs. *Proceedings of National Academy of Sciences, USA* **2016**, 113, 152–157.
34. McParland S.; Kearney F.; Berry D.P. Purging of inbreeding depression within the Irish Holstein-Friesian population. *Genet. Sel. Evol.* **2009**, 41, 16.
35. Mellersh C. Give a dog a genome. *Vet. J.* **2008**, 178, 46-52.

36. Oberbauer, A.; Keller, G.; Famula, T. Long-term genetic selection reduced prevalence of hip and elbow dysplasia in 60 dog breeds. *PLoS ONE*. **2017**, *2*:e0172918.
37. Peterson, C. Canine hip dysplasia: Pathogenesis, phenotypic scoring, and genetics. *Dul. J. Undergr. Biol.* **2017** *4*, 19-27.
38. de la Riva, G.T.; Hart B.L.; Farver, T.B.; Oberbauer, A.M.; Messam, L.L.M.; Willits, N.; Hart, L.A. Neutering dogs: effects on joint disorders and cancers in golden retrievers. *PLOS ONE*, **2013**, *8*(2):e55937 10.1371.
39. Suwanlee, S.; Baumung, R.; Solkner, J.; Curik, I. Evaluation of ancestral inbreeding coefficients: Ballou's formula versus gene dropping. *Cons. Genet.* **2007**, *8*, 489– 495.
40. Todd, E.T.; Ho, S.Y.W.; Thomson, P.C.; Ang, R.A.; Veile, B.D.; Hamilton, N.A. Founder specific inbreeding depression affects racing performance in thoroughbred horses. *Scientific Reports*, **2018**, *8*, 6167,
41. Urfer, S.R.; André, A.; Steiger, A.; Gaillard, C.; Creevy, K.E.; Kaeberlein, M. Promislow, D. Pedigree Analysis of a Large Dog Population. *Population, Evolutionary, and Quantitative Genetics Conference*. Madison, **2018**, WI; p. 1,
42. Wellmann, R., Pfeiffer, I. Pedigree analysis for conservation of genetic diversity and purging. *Genetics Research*, **2009**, *91*, 209–219,