Improvements in Genetic Selection Against Canine Hip Dysplasia Using Index Methodology

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Introduction

The extent of inherited disease in pedigree dog breeds has recently come under scrutiny (Higgins and Nicholas, 2008) and the potential role of genetic selection in tackling such disease has been recognised (Lohi and Nicholas, 2009). Hip dysplasia is one of the most important complex genetic diseases in dogs since it is the most prevalent disease among larger breeds. It is characterised by the formation of a loose, ill-fitting coxofemoral (hip) joint (Brass, 1989) which leads to the abnormal wearing of bone surfaces and, over time, the appearance of signs of osteoarthritis (OA) (Maki, 2004). The OA that develops is irreversible and therefore reduction in the prevalence of hip dysplasia through genetic selection is the only method available to provide a lasting and widespread improvement in the welfare of susceptible breeds.

Several evaluation programmes are in operation due to the prevalence and seriousness of hip dysplasia. The British Veterinary Association (BVA) / Kennel Club (KC) scoring scheme, which was established in its current form in 1984 (Gibbs, 1997), is used in the UK, Ireland, Australia and New Zealand. The rate of participation in the UK is good; with, for example, 8-10% of all annually registered Labrador Retrievers (the most popular breed in the UK with ~45 000 annual registrations) scored per year, equating to 50-60% of all dogs used for breeding. Thus, data from the BVA/KC scoring scheme is a valuable resource in tackling hip dysplasia.

Researchers have a responsibility to make the best use of the available data to reduce the disease burden across pedigree dog breeds through effective and efficient genetic selection. Selection index theory provides such a method to determine the selection coefficients of traits that will result in optimal progress towards a set selection objective. Comparison of the accuracy of the optimal selection coefficients with those currently being applied demonstrate the potential progress that may be attained simply by improving application of the available data.

Material and methods

BVA/KC Hip Score methodology

Radiographs of the pelvic area are taken according to standardised protocols, submitted to the BVA and scored by three members of a panel of certified veterinarians on nine features of the

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hip joint: Norberg angle (NA), subluxation (SUB), cranial acetabular edge (CrAE), dorsal acetabular edge (DAE), cranial effective acetabular rim (CrEAR), acetabular fossa (AF), caudal acetabular edge (CAE), femoral head and neck exostosis (FHNE) and femoral head recontouring (FHR). Eight of the nine features are scored out of six for each hip, and the ninth is scored out of five for each hip (zero being a valid score indicating no signs of dysplasia). The total summed score ranges from zero to 106 and is considered to describe the general condition of the dog's hip joints. Six of the nine features are scored exclusively on the detection of pathological signs of OA (DAE, CrEAR, AF, CAE, FHNE, FHR), two of the features are scored exclusively on morphology (NA, SUB), and one feature is scored on a mixture of both (CrAE).

Data and Pedigree

Data consisted of individual left and right hip scores of NA, SUB, CrAE, DAE, CrEAR, AF, CAE, FHNE and FHR for 11,928 Labrador Retriever dogs scored through the BVA/KC scheme (computerised records were kindly provided by Dr Malcolm Willis). All dogs were between 1 and 4 years old when scored, and were scored between 2000 and 2007. Pedigree information was provided by the KC.

Calculation of Genetic Parameters

The phenotype of each of the nine traits was the untransformed sum of scores of left and right hips since previous analysis had determined substantial genetic similarity of left and right hip scores. (Co)variance estimates for the nine traits were calculated using 9 univariate and 36 pairwise bivariate linear mixed models, fitted with ASREML. Sex, age at score, season of birth and year of score were included as fixed effects; animal and litter were included as random effects. From these analyses the phenotypic (***P***) and genotypic (***G***) matrices were constructed. ***G*** was made positive definite by the substitution of two small, negative eigenvalues by small, positive values.

Selection Index methodology

Optimum selection indices for selection objectives (*H*) using the selection criteria (*I*) were obtained, with coefficients (***b***) calculated as $\boldsymbol{b} = \boldsymbol{P}_{II}^{-1} \boldsymbol{G}_{IH} \boldsymbol{a}$. Here, subscripts *I* and *H* define the relevant sub-matrices of ***P*** and ***G*** for traits in *I* and in *H*, and ***a*** represents the vector of relative values for traits in the objective defining the aggregate breeding value. The accuracy of the selection index was determined as the correlation of the aggregate breeding value with the index value.

Optimum indices for different ***a*** were considered: (i) $a_i = 1/\sigma_{Pi}$ for trait i, so attaching equal value to the traits when standardised phenotypically; (ii) $\boldsymbol{a} = [1\ 1\ 1\ 1\ 1\ 1\ 1\ 1\ 1]^T$, so the aggregate breeding value is the breeding value for the total hip score; and (iii) $\boldsymbol{a} = [0\ 0\ ½\ 1\ 1\ 1\ 1\ 1\ 1]^T$, so the aggregate breeding value is a measure of propensity for pathological damage, which might be considered to better reflect welfare.

For each value of ***a***, the accuracy of the optimum index was compared to current selection practice which uses the total hip score as represented by $\boldsymbol{b}^T$=[1 1 1 1 1 1 1 1 1], the aggregate score of only morphological traits represented by $\boldsymbol{b}^T$=[1 1 1 0 0 0 0 0 0] (NA+SUB+CrAE) or

$\boldsymbol{b}^T$=[1 1 0 0 0 0 0 0 0] (NA+SUB), and the aggregate score of entirely pathological traits represented by b^T=[0 0 0 1 1 1 1 1 1] (DAE+CrEAR+AF+CAE+FHNE+FHR).

Results and discussion

Phenotypic and additive genetic variance, heritability and litter effects for all nine traits are shown in Table 1. Phenotypic and genetic correlations were all positive, favourable and high (r_P ranging from 0.47-0.88 and r_A ranging from 0.70-0.99). Morphological traits were notably higher in heritability.

Table 1: Estimates of phenotypic and additive genetic variance, heritability and litter effect for the nine traits that constitute total BVA/KC hip score.

Traits	σ^2_P	σ^2_A	h^2	litter effect
NA	7.61 ±0.12	2.82 ±0.23	0.37 ±0.03	0.08 ±0.02
SUB	3.04 ±0.05	1.14 ±0.09	0.38 ±0.03	0.10 ±0.02
CrAE	1.42 ±0.02	0.30 ±0.03	0.21 ±0.02	0.06 ±0.02
DAE	2.88 ±0.04	0.52 ±0.07	0.18 ±0.02	0.06 ±0.02
CrEAR	2.47 ±0.04	0.51 ±0.06	0.21 ±0.02	0.09 ±0.02
AF	1.80 ±0.03	0.28 ±0.04	0.15 ±0.02	0.08 ±0.02
CAE	1.32 ±0.02	0.19 ±0.03	0.15 ±0.02	0.04 ±0.02
FHNE	2.95 ±0.04	0.70 ±0.08	0.24 ±0.03	0.07 ±0.02
FHR	1.26 ±0.02	0.24 ±0.03	0.19 ±0.03	0.04 ±0.02

As expected the use of optimised selection coefficients for $\boldsymbol{b}$ using information on all 9 traits, when appropriately weighted, always gave the highest accuracies for all *H* (see Table 2). When $\boldsymbol{a}$ includes all nine traits in *H* and attaches equal importance to the standardised phenotypic variation in each of the traits, the selection coefficients in $\boldsymbol{b}$ are: 0.538 (NA), 0.546 (SUB), 0.12 (CrAE), -0.184 (DAE), -0.126 (CrEAR), -0.310 (AF), -0.186 (CAE), 0.371 (FHNE), 0.564 (FHR). This profile is qualitatively similar for other values of $\boldsymbol{a}$. The negative coefficients do not imply selection for features definitive of dysplasia, but rather signify that some traits act as 'environmental corrections' to more informative trait(s) that are richer in genetic information allowing better prediction of total genetic merit.

Table 2 shows the inclusion of all nine traits in *I* was only 1.02-fold more accurate than using only NA, SUB and CrAE when *H* attached importance to morphology, and only 1.04-fold more accurate when H was focused upon pathology. The difference with the optimum remained similar when the index traits were further reduced to include only the purely morphological traits NA and SUB. If only pathology traits were used in the index for prediction of genetic merit then the accuracies were much lower. For example, even when the objective *H* is focused upon pathology, the accuracy obtained when excluding the morphology is only 0.78 of the optimum index including the morphology (0.60 vs 0.46). This establishes the predictive value of the morphological traits for the genetics of the pathology associated with hip dysplasia. Their effectiveness arises from their relatively high heritabilities and their high genetic correlations with the pathology traits (values not shown).

Current selection progress relies on mass selection using the total score which, as noted above, is equivalent to $\boldsymbol{b} = [1111\ldots1]^T$. Table 2 shows that accuracies using the total score are only 0.88 to 0.90 of the optimum depending on the values in $\boldsymbol{a}$. In fact the total score does worse than using only morphology. This seems counter intuitive since it appears as if information is being thrown away. The explanation is that adding the pathology traits to the morphology traits with equal weight is adding relatively more error variation since they are less heritable whilst being highly correlated genetically. Heuristically, the index $\boldsymbol{b} = [1110\ldots0]^T$ is 'closer' to the optimum selection index (coefficients given above) than the total score for those traits richest in genetic information.

Table 2: Accuracies from selection indices with different coefficients (*b*) (from left to right: the optimum, aggregate total hip score, aggregate NA+SUB+CrAE, aggregate NA+SUB, aggregate DAE+CrEAR+AF+CAE+FHNE+FHR), and at different weights (*a*) (from top down: scaled and equal, unscaled and equal, and weighted on impact on OA).

Values (***a***)	Selection coefficients (***b***)				
	Optimum	$[1111\ldots1]^T$	$[1110\ldots0]^T$	$[1100\ldots0]^T$	$[0001\ldots1]^T$
$1/\sigma_{Pi}$	0.616	0.545	0.598	0.602	0.456
$[1111\ \ldots\ 1]^T$	0.619	0.545	0.603	0.609	0.454
$[00½1\ \ldots\ 1]^T$	0.595	0.537	0.570	0.573	0.462

Conclusion

Hip dysplasia is the most widespread inherited disease of dogs and genetic selection is the only method available to reduce the disease burden. The results demonstrate that substantial improvements in selection accuracy against hip dysplasia over current practice can be made through the application of simple selection index methods. Rates of genetic gain are directly related to accuracy and those presented here are the most relevant to current practice, since mass selection is the only tool available to the breeder in the UK. Therefore, the rate of genetic progress against hip dysplasia in the most common breed of pedigree dog in the UK could be increased by 10 to 12% simply by re-weighting the information already collected on each individual.

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