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How the Orthopedic Foundation for Animals (OFA) is tackling inherited disorders in the USA: Using hip and elbow dysplasia as examples

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ABSTRACT

The Orthopedic Foundation for Animals (OFA) maintains an on-line health pedigree database for inherited disorders of animals. With the American Kennel Club Canine Health Foundation, the OFA maintains the Canine Health Information Center (CHIC) for parent breed clubs to identify breed-specific required health tests. Analysis of the results of OFA evaluations in the hip and elbow registries show that selection based on phenotype improves conformation. Disorders with complex inheritance respond best to selection based on depth (ancestors) and breadth (siblings) of pedigree health test results. This information can be derived from vertical pedigrees generated on the OFA website.

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Introduction

A prominent businessman in the United States, John M. Olin, was also an avid sportsman and recognized the impact of canine hip dysplasia on his Labrador retrievers. Along with the Golden Retriever Club of America, German Shepherd Club of America and the veterinary community, he organized a meeting that eventually led to the formation of the Orthopedic Foundation for Animals (OFA) in 1966. The OFA is guided by the following four specific objectives:

(1) To collate and disseminate information concerning orthopedic and genetic diseases of animals.
(2) To advise, encourage and establish control programs to lower the incidence of orthopedic and genetic diseases.
(3) To encourage and finance research in orthopedic and genetic disease in animals.
(4) To receive funds and make grants to carry out these objectives.

The OFA is governed by a voluntary Board of Directors. As a not-for-profit organization, the revenue over expenses is either held in the operating reserve or donated to support animal health-related research. Most funding is channeled through the American Kennel Club Canine Health Foundation (AKC-CHF)[1] or Morris Animal Foundation, with occasional direct funding. OFA has supported research not only in orthopedic diseases but also for cancer, cardiac, hepatic, nephritic, neurologic, ocular and thyroid disease.

While the OFA's initial focus was canine hip dysplasia, the mission has broadened to include cats and other genetic diseases, including elbow dysplasia, patella luxation, autoimmune thyroiditis, congenital heart disease, Legg–Calve–Perthes disease, osteochondrosis dissecans (shoulder osteochondrosis), sebaceous adenitis and congenital deafness. The methodology and criteria for evaluating the test results for each disorder are independently established by veterinary scientists from their respective specialty areas and the standards used are generally accepted throughout the world. Disorders present on the OFA website include those that have a defined test for normalcy. Disorders such as epilepsy, gastric dilatation/volvulus and cancers that do not have defined phenotypic or genotypic tests are not included. If genetic markers for disease liability are identified in the future, these can be added as tools for genetic disease control.

The power of the OFA genetic database lies in the compilation and integration of all health screening information in a single location. For dogs with an existing OFA record, examination results from the Canine Eye Registry Foundation (CERF) are incorporated in their OFA record. In addition, the results of genotypic tests that are either submitted by the owner or through a cooperative agreement with the parent club are also included in the OFA genetic database. Cutting-edge advancements in molecular genetics now account for over 90 DNA tests involving over 145 breeds of dogs and cats.

The collection of such data is meaningless unless the data can be disseminated to parties of interest. The OFA maintains an

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[1] See: www.akcchf.org.

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on-line database of >1 million phenotypic and genotypic test results.[2] All normal or grades of normal results in the OFA database are available on-line. Abnormal or grades of abnormal results are available on-line if released by the owner, or if the results are part of a breed club program where all (normal and abnormal) test results are published.

The Canine Health Information Center (CHIC)[3] is a program that is dually sponsored by the OFA and the AKC-CHF. The parent clubs determine the breed-specific health issues for CHIC certification and encourage breeder participation in the program. The CHIC program is not about normalcy; it is about health consciousness. Dogs receive CHIC certification if they have completed the required breed-specific health testing, regardless of the test results. Other requirements include permanent identification (tattoo or microchip) and release to the open database of abnormal results. CHIC encourages health screening to improve the overall health of breeds. There are presently over 139 parent breed clubs participating, with over 64,500 dogs achieving CHIC certification.

The acceptance of the CHIC certification program by parent breed clubs and breeders provides an avenue for the only proven method of genetic disease control: breed-specific phenotypic and genotypic screening of prospective breeding stock. The CHIC program provides a standard for breeders to practice health-conscious breeding. It also allows pet owners to screen prospective purchases for evidence of health-conscious breeding.

Another goal of the CHIC program is to collect and store canine DNA samples, along with corresponding genealogic and phenotypic information, to facilitate future research and testing aimed at reducing the incidence of inherited disease in dogs. Researchers have been hampered by the lack of appropriate DNA samples and the DNA repository addresses this need. To date, the CHIC DNA Repository contains DNA from over 12,500 dogs and has received 17 requests from researchers, resulting in the distribution of over 2,200 DNA samples with their appropriate health and pedigree information.

To evaluate hip dysplasia, the OFA employs the ventrodorsal hip-extended positioning recommended by the American Veterinary Medical Association (AVMA Council on Veterinary Service, 1961). The in-house radiologist is the sole evaluator for preliminary evaluation of dogs <24 months of age. The reliability of preliminary hip evaluations for predicting of-age OFA ratings was demonstrated by Corley et al. (1997). Dogs or cats must be $\geqslant$24 months of age to receive OFA hip certification. Radiographs are independently evaluated by three board-certified veterinary radiologists out of a pool of consultants maintained by the OFA. The consensus rating of these three radiologists becomes the hip rating that is reported to the owner and referring veterinarian. There is a high degree of inter- and intra-reader correlation for conventional and digital images (Corley, 1992; Essman and Sherman, 2006).

Seven OFA hip ratings are reported: Excellent, Good, Fair, Borderline, Mild, Moderate or Severe. The first three ratings are considered to be normal, while the last three ratings are regarded as dysplastic. A Borderline rating is given when there is no clear consensus between radiologists to place the hips in a category of normal or dysplastic. It is recommended that dogs with this rating have a repeat radiograph submitted after a minimum of 6 months.

The OFA elbow dysplasia registry employs the protocol established by the International Elbow Working Group (IEWG),[4] which consists of Normal or Grades I, II or III Dysplastic based on the severity of secondary osteoarthritis/degenerative joint disease present on an extreme flexed mediolateral view (International Elbow Working Group, 2001). When a specific component of elbow dysplasia is observed, it is reported in addition to the Grade as ununited anconeal process, osteochondrosis or fragmented medical coronoid process. Elbow radiographs are subjected to the same of-age or preliminary evaluation and certification process as hip radiographs.

Diseases with complex inheritance can respond to selective pressure based on phenotype (Keller, 2006; Pirchner, 1983). In this manuscript, the OFA hip and elbow registries are used to illustrate this response.

Materials and methods

The OFA hip registry of 1,187,831 evaluations was queried for hip ratings of progeny where both parents also had known of-age hip ratings. Data were collected on progeny with of-age or preliminary hip confirmation ratings of normal (Excellent, 1; Good, 2; Fair, 3) or dysplastic (Mild, 5; Moderate, 6; Severe, 7). Progeny with Borderline (4) hip ratings were not included. The hip ratings of both parents were recorded, including all seven grades. A hip Combined Parent Score (CPS) for each mating was determined by adding together the numbers corresponding to the hip rating for each parent; for two OFA Excellent parents the CPS was 2 and for two OFA Severe parents the CPS was 14. Matings with the same CPS were combined together for analysis; e.g. Good mated to Borderline, Fair mated to Fair and Excellent mated to Mild all have a CPS of 6.

The OFA elbow registry of 260,195 evaluations was queried for elbow ratings of progeny where both parents had known of-age elbow ratings. Data were collected on progeny with preliminary or of-age elbow confirmation ratings of Normal (1) or dysplastic (Grade I, 2; Grade II, 3; Grade III, 4). An elbow CPS for each mating was determined by adding together the numbers corresponding to the elbow rating for each parent; for two OFA Normal parents the CPS was 2 and for two OFA Grade III parents the CPS was 8. Matings with the same CPS were combined together for analysis.

Pearson correlation analysis was performed to compare the CPS of matings to the observed percentages of hip dysplasia or elbow dysplasia in the progeny.

Results

Table 1 shows the hip ratings for 490,966 progeny in the OFA hip registry with known sire and dam hip ratings. The percentage of dysplastic progeny increased as the parental hip scores increased. The total number of hip radiograph submissions from parents with normal hip ratings was significantly greater than those from parents with dysplastic hip ratings ($P > 0.05$).

Fig. 1 shows the relationship between the CPS and the percentage of dysplastic progeny. Matings with the same CPS (on the diagonal of Table 1) were strongly correlated with increasing percentages of dysplastic progeny (Pearson correlation coefficient $r = 0.96$; $P > 0.05$). The single CPS that did not reflect this trend was for matings between two severely dysplastic parents, where only 18 progeny were submitted for evaluation.

Table 2 shows the elbow ratings for 67,599 progeny in the OFA elbow registry with known sire and dam elbow ratings. Matings including one normal parent had significantly lower percentages of progeny with elbow dysplasia (12.4%) than those between two parents with elbow dysplasia (45.4%) ($P > 0.05$). Matings involving a parent with Grade I elbow dysplasia produced significantly more elbow dysplasia (25.6%) than matings including a parent with normal elbows ($\chi^2 = 0.77$, 6 df, $P = 0.99$).

Fig. 2 shows the relationship between the CPS and the percentage of progeny with elbow dysplasia. The Pearson correlation coefficient between the CPS and percentage of dysplastic progeny was $r = 0.06$. The lack of correlation is due to the low percentage of dysplasia in progeny of Grade III sires bred to Grade II dams, and Grade III parents bred to each other. The total number of progeny from these matings numbered 14 and 3, respectively.

Discussion

The OFA hip data and CPS demonstrate that hip dysplasia is inherited in an additive and quantitative manner. This verifies

[2] See: www.offa.org.
[3] See: www.caninehealthinfo.org.
[4] See: www.iewg-vet.org/.

Table 1
Progeny results of matings between parents with known hip scores.

Sire rating	Dam rating							Total
	Excellent (1)	Good (2)	Fair (3)	Borderline (4)	Mild (5)	Moderate (6)	Severe (7)	
Excellent (1)								
Dysplastic (%)	3.6	6.1	9.6	12.3	13.4	18.7	18.5	
Total	17,972	52,784	9039	155	1271	729	65	82,015
Good (2)								
Dysplastic (%)	5.8	9.6	14.6	17.5	18.9	23.0	31.5	
Total	50,485	217,938	49,212	811	6930	3973	461	329,810
Fair (3)								
Dysplastic (%)	9.4	14.1	19.8	22.8	26.5	32.2	37.1	
Total	6241	41,628	13,513	263	2301	1328	167	65,441
Borderline (4)								
Dysplastic (%)	8.9	17.7	20.2	22.2	30.8	50.0	50.0	
Total	79	532	168	9	39	30	4	861
Mild (5)								
Dysplastic (%)	16.4	18.3	27.2	36.2	29.6	41.4	45.0	
Total	807	4531	1532	47	459	239	40	7655
Moderate (6)								
Dysplastic (%)	18.9	22.8	31.6	34.4	35.0	38.0	65.3	
Total	428	2618	896	32	266	213	49	4502
Severe (7)								
Dysplastic (%)	22.0	24.2	36.0	44.4	39.6	55.8	44.4	
Total	59	360	136	9	48	52	18	682
Total	76,071	320,391	74,496	1326	11,314	6564	804	490,966

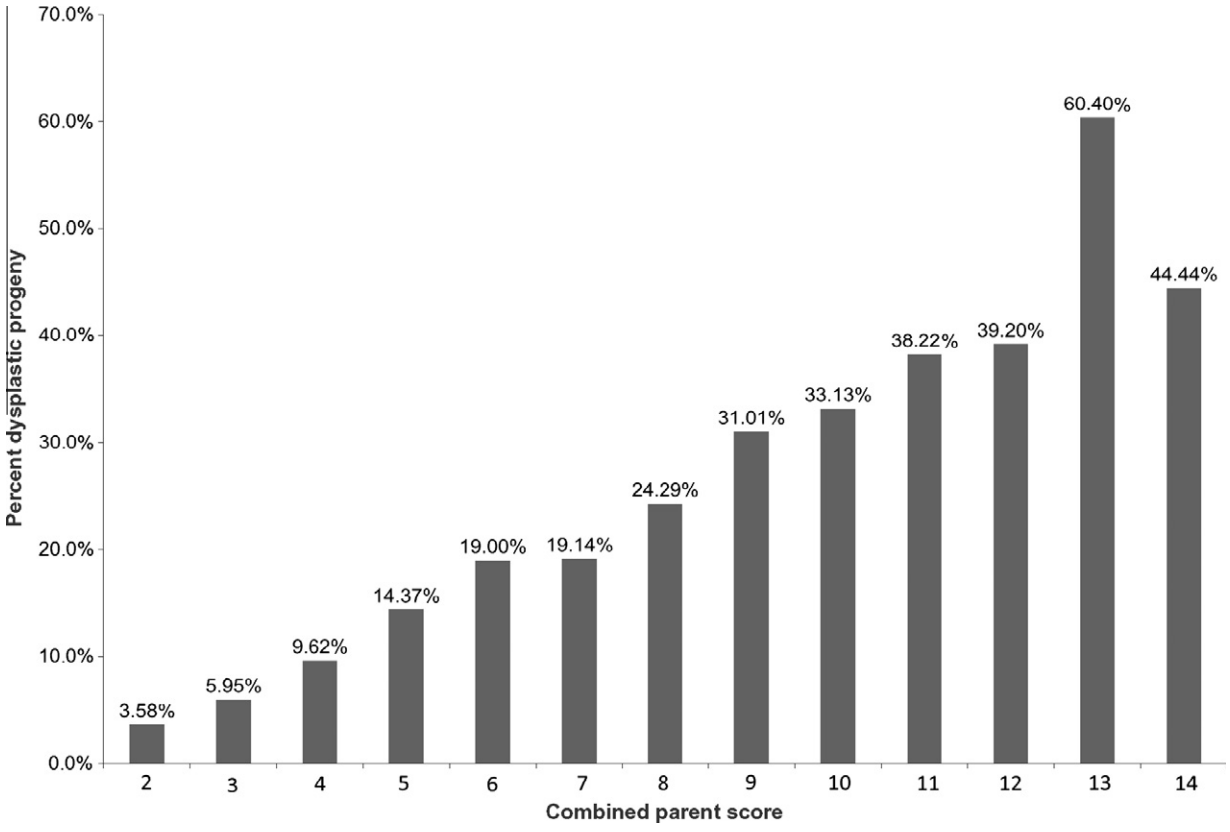

Fig. 1. Relationship of Combined Parent Score to percentage of hip dysplastic progeny.

the conclusions of other researchers that canine hip dysplasia is inherited as a quantitative trait (Leighton, 1997; Zhu et al., 2009; Hou et al., 2010). Hou et al. (2010) analyzed all Labrador retrievers in the open-access OFA hip database and calculated an heritability of 0.21, which confirms hip dysplasia acting as a moderately heritable disease. They also confirmed a steady genetic improvement of OFA hip ratings in the breed over a 40 year period. These results validate the OFA recommendation that using parents with better phenotypic hip conformation produces offspring with better hips.

It was expected that fewer radiographs would be submitted for the progeny of two dysplastic parents, since fewer breeders perform such matings. The low numbers may also be due to pre-

Table 2
Progeny results of matings between parents with known elbow scores.

Sire rating	Dam rating				Total
	Normal (1)	Grade I (2)	Grade II (3)	Grade III (4)	
Normal (1)					
Dysplastic (%)	10.1	24.1	29.4	28.1	
Total	55,867	4309	875	167	61,218
Grade I (2)					
Dysplastic (%)	22.0	41.0	46.9	52.2	
Total	3917	591	145	23	4676
Grade II (3)					
Dysplastic (%)	32.6	55.4	65.8	57.1	
Total	1121	222	38	14	1395
Grade III (4)					
Dysplastic (%)	23.9	38.1	14.3	0.0	
Total	251	42	14	3	310
Total	61,156	5164	1072	207	67,599

screening of radiographs with obviously dysplastic hips by veterinarians; these radiographs may not be submitted to the OFA for evaluation (Paster et al., 2005). This would reduce the resultant frequencies of dysplastic individuals. Prescreening of dysplastic radiographs for OFA submission appears to be constant over time (Reed et al., 2000).

Traits such as hip dysplasia and elbow dysplasia are complexly (polygenically) inherited, with increasing incidence based on increasing frequencies of susceptibility alleles at loci that contribute to variation in liability. Selection based on vertical or depth-of-pedigree hip ratings (parents and grandparents), when combined with an individual's own rating, increases the accuracy of selection and hence response to selection. Similarly, selection based on horizontal or breadth-of-pedigree hip ratings (siblings), when combined with an individual's own rating, increases accuracy of selection and hence response to selection (Pirchner, 1983; Keller, 2006).

Breeding schemes that employ estimated breeding values (EBVs) that combine phenotypic ratings from all known relatives (weighted according to genetic relationship) provide the greatest selective power, rather than single measurements on individual dogs (Zhu et al., 2009; Hou et al., 2010). EBVs that utilize molecular genetic markers for liability genes would be even more beneficial (Stock and Distl, 2010; Zhou et al., 2010).

The open-access OFA health database website provides breeders with the information that helps them to make informed breeding decisions. When an individual dog's record is accessed, detailed information on all recorded health issues, including test results, age at the time of testing and the resulting certification numbers, are available. Sire and dam information are provided, as well as information on full and half siblings and any offspring that may be in the database. A vertical pedigree can be generated from a link on the individual's OFA page, providing traditional depth of pedigree and breadth of pedigree health information. This type of data is extremely useful when trying to make selection decisions based on phenotypic data.

The vertical hip pedigree of the Golden retriever Champion (Ch.) Faera's Starlight (Fig. 3) shows how parent, grandparent, offspring and sibling information are combined in a single graphic format for evaluation. Whilst this dog had hips with an Excellent rating, he was bred from Fair- and Good-rated parents, with three Fair- and one Good-rated grandparents. While he produced 92.4% normal offspring with a preponderance of Good ratings, he produced more Fair- than Excellent-rated offspring. The vertical pedigree provides more information than the single individual rating. Vertical

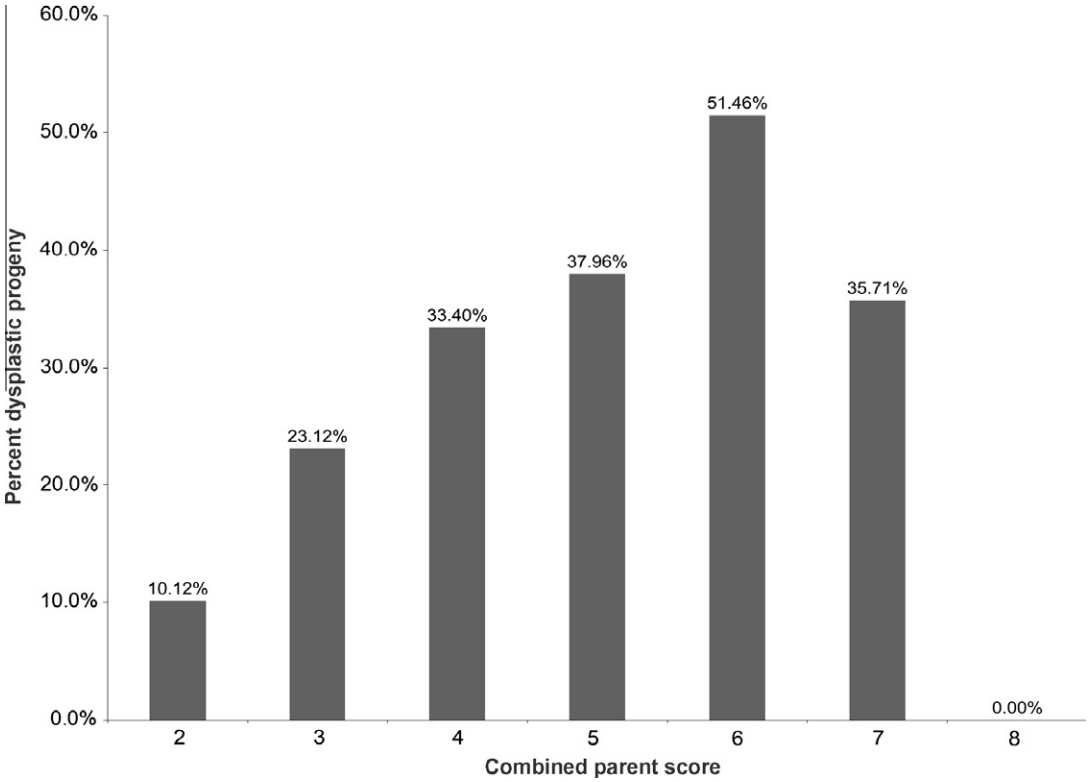

Fig. 2. Relationship of Combined Parent Score to percentage of elbow dysplastic progeny.

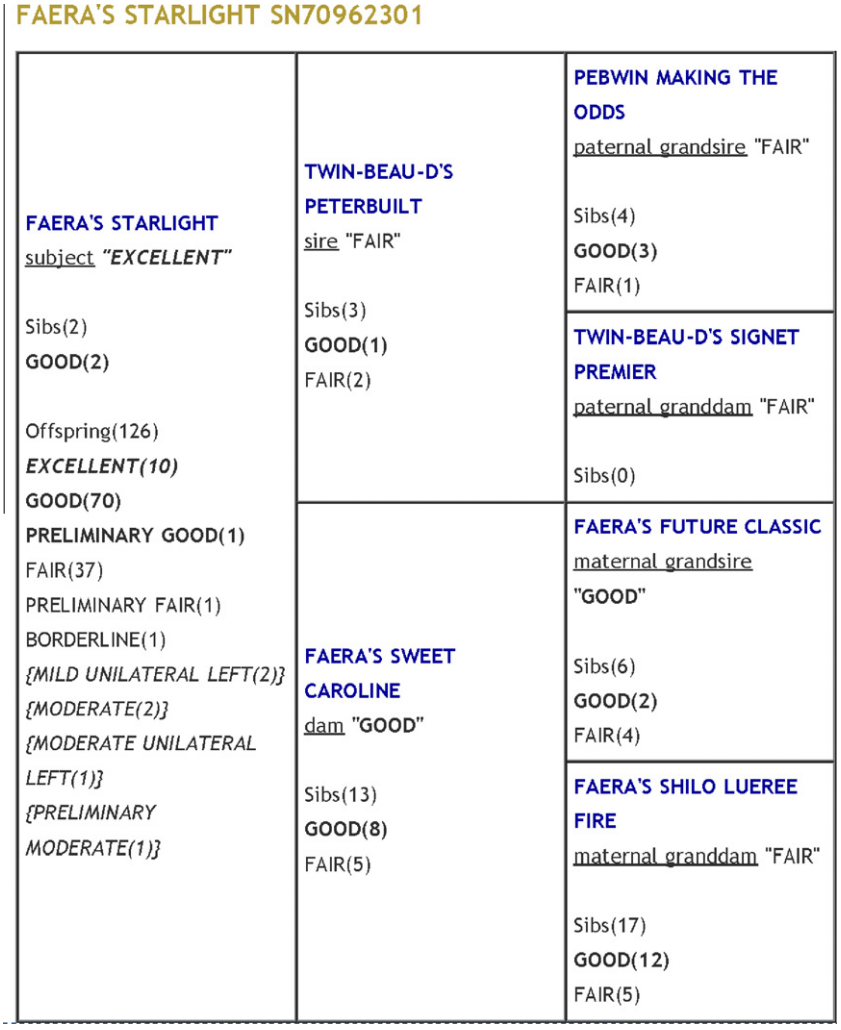

Fig. 3. OFA vertical pedigree of Golden retriever Ch. Faera's Starlight.

pedigrees of individual animals are available on the OFA website for the hip, elbow, cardiac, thyroid, patella, CERF (eye) and degenerative myelopathy registries.

EBV technology would combine all of the phenotypic information in Fig. 3 into a single measurement that provides the most accurate possible prediction of the average performance of the offspring of the dog in question (Faera's Starlight). However, the individual's OFA page and vertical pedigree allows the breeder to determine where the liability comes from in the pedigree, the specific results from each mating and each dog's strengths and weaknesses. These are useful tools for selection and genetic improvement.

The distraction index (DI) measurement of the PennHIP method for hip dysplasia control employs a mechanical distraction device to measure maximal hip joint laxity as a predictor of future degenerative joint disease and osteoarthritis (Smith et al., 1990). PennHIP studies show that the OFA rating and DI measurement are significantly associated (Powers et al., 2010) and DI measurements submitted by their owners to the OFA are included in the hip dysplasia registry.

While the DI provides a measurement of laxity, it does not take into account degenerative joint disease or osteoarthritic changes. Studies have shown that liability for hip dysplasia and liability for osteoarthritis are controlled by separate genes (Clements et al., 2006; Zhou et al., 2010). The OFA hip rating incorporates an evaluation of both subluxation on the ventrodorsal hip-extended view, as well as radiographic anatomy and secondary boney changes.

The PennHIP method recommends selection based on the DI measurement of individual dogs. Based on PennHIP data of dogs presented to the University of Pennsylvania School of Veterinary Medicine, 100% of Golden retrievers and 89% of Labrador retrievers who received normal OFA ratings were deemed osteoarthritis-susceptible by their DI (Powers et al., 2010). Powers et al. (2010) also raised the possibility that the Cardigan Welsh Corgi is genetically fixed for hip dysplasia, based on DI measurements for the breed. However, the clinical presentation of disease in these breeds does not bear out these predictions, suggesting that there is a high false-positive rate for DI prediction of clinical disease. A study correlating ventrodorsal hip-extended radiographic ratings to later insurance-related claims for hip dysplasia showed a strong association (Malm et al., 2010). Data correlating DI measurements to morbidity from clinical disease have not been published.

Dog breeds have closed stud books and dog breeders have concerns about genetic diversity and the effects of artificial selection on their gene pools (Calboli et al., 2008). The removal of 89% or more of possible breeding stock for a single genetic disorder (which would be required in order to breed only from those Labrador retrievers with acceptable DI) will doom any breed to extinction from genetic depletion. While breeding from only OFA

Excellent dogs will significantly improve hip ratings of progeny, the elimination of the rest of the phenotypically normal dogs from breeding (most of which produce predominantly normal dogs) would also severely restrict the gene pools of breeds. Pragmatic breeding recommendations include breeding from normal dogs with increasing normalcy of parents, grandparents, siblings and progeny, as shown on the OFA vertical pedigree, and through the use of EBVs.

The significant difference between progeny from one parent with normal elbows and progeny from two parents with dysplastic elbows suggests a qualitative trait. However, it is established that elbow dysplasia is a polygenic (multifactorial) trait (Engler et al., 2009). Increasing CPS tended to increase the frequency of elbow dysplasia in the progeny, but low numbers of submissions for some mating types between dysplastic parents skewed the results, making the correlation inconclusive. Again, pre-screening and non-submission to OFA of obviously dysplastic radiographs may have affected the data.

Grade I elbow dysplasia is a radiographic diagnosis that usually does not produce clinical disease or morbidity in the dog. Some breed groups counsel owners to ignore the diagnosis of Grade I elbow dysplasia and to treat these dogs as if they were normal. However, the data presented here demonstrates that progeny from a parent with Grade I elbow dysplasia, when bred to mates from all other rating classifications, have a significantly increased frequency of elbow dysplasia. These results are significantly different from the results observed with progeny from one normal parent bred to mates from all other rating classifications.

The data show that even two dogs with normal elbow radiographs may produce 10.1% progeny with elbow dysplasia. This is where consideration of depth and breadth of pedigree information becomes important. Any rating of elbow dysplasia in siblings of dogs with a normal elbow rating provides evidence that the normal dog may carry additional elbow dysplasia liability alleles.

Selection for increasing normalcy of depth and breadth of pedigree information provides a better selection tool for complexly inherited disease. The use of the OFA vertical pedigree provides the information necessary to make informed breeding decisions. The addition of EBVs that combine all of this information (Engler et al., 2009) and that also include genotypes of DNA markers for liability genes (Stock and Distl, 2010; Zhou et al., 2010) would be even more beneficial.

Conclusions

The OFA data show that hip and elbow conformation improve with improving parental phenotypic ratings. The open access OFA website provides health test results on individuals, as well as depth and breadth of pedigree health information on closely related individuals. This information provides the best means for making breeding decisions for both complexly inherited and Mendelian disorders.

Conflict of interest statement

The authors are Chief of Veterinary Services (GGK), Chief Operating Officer (ED) and Director (JSB) of the not-for-profit Orthopedic Foundation for Animals.

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