Worldwide Screening for Canine Hip Dysplasia: Where Are We Now?

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Objective: To critically review the different screening systems used for canine hip dysplasia (CHD) and their impact on the prevalence of the disease.
Study design: Critical literature review.
Methods: Literature search through PubMed (November 1959–October 2011) and the Orthopedic Foundation for Animals (OFA), Fédération Cynologique Internationale (FCI), British Veterinary Association/Kennel Club (BVA/KC), and Pennsylvania Hip Improvement Program (PennHIP) websites.
Results: The OFA, FCI, and BVA/KC screening methods, which use the hip-extended radiographic projection, have had relatively minor success on CHD prevalence. These screening approaches are prone to conflicting data regarding interobserver agreement. The PennHIP and Dorsolateral Subluxation (DLS) systems, both distraction methods, have not reported on prevalence but seem to be important heritable traits in genomic screening of dysplastic dogs.
Conclusion: A shift towards genome screening yields a promising future combating CHD, although further investigation towards fine-mapping in the search for genes, responsible for CHD, is necessary.

The Orthopedic Foundation for Animals (OFA), Fédération Cynologique Internationale (FCI), British Veterinary Association/Kennel Club (BVA/KC), Pennsylvania Hip Improvement Program (PennHIP), and Dorsolateral Subluxation Score (DLS) are the 5 most widespread and thoroughly investigated screening approaches for canine hip dysplasia (CHD). The primary goal for each screening program is to exclude genetically burdened individuals from the breeding pool. Because CHD is a polygenetic heritable trait,[1] and current screening systems rely on interpretation of radiographs, their efficacy reducing CHD is limited.[2–4] Despite intensive screening for 4 decades, the prevalence of CHD is still as high as 40% in some breeds.[5]

Accurate quantification of radiographic phenotypic criteria remains difficult and is subject to various factors affecting standardization, even in the numerical semiquantitative BVA/KC system.[6] Furthermore, the OFA and FCI screening systems use descriptive criteria to score hips, which is even more subjective. In an attempt to quantify hip joint conformation and laxity, the Norberg angle (NA) measurement and the application of stress radiographs in the PennHIP and DLS methods seem to generate more promising results from radiographic interpretation.[7–10] However, complete eradication of CHD based on phenotypic criteria remains difficult, even with accurate numerical data obtained from radiographs. As long as dysplastic dogs are used for breeding and only a biased and small selection of progeny is tested, impact on CHD prevalence remains low. In this overview, the OFA, FCI, BVA/KC, PennHIP, and DLS methods are described briefly and their impact on CHD prevalence is reported.

The Orthopedic Foundation for Animals (OFA)

The OFA has been screening dogs for CHD since 1966 and is used in the United States and Canada. In dogs $\geq$ 24 months old, using standard hip-extended radiographs, a descriptive 7-point scoring method is used with hips graded as excellent, good, fair, borderline, mild CHD, moderate CHD, and severe CHD.[11] Radiographic criteria that focus on the hip joint conformation (signs of incongruence and degenerative joint disease [DJD]) and hip joint laxity are considered. The scoring system does not use the NA measurement. Chemical restraint is not mandatory but is recommended for muscle relaxation. Dogs with grades of excellent, good, and fair are considered as nondysplastic, whereas those with mild, moderate, or severe CHD are considered dysplastic. If none of these grades are applicable: the dog is considered borderline and these dogs are re-evaluated in 6 months.

Three independent board-certified radiologists with extensive experience in CHD interpretation evaluate the radiographs. Only if there is interobserver consensus, are the results reported to the owner. If 2 of 3 radiologists report

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the same grade, the dog receives that grade. If 1 radiologist grades a dog as excellent, 1 good, and 1 fair, the dog is graded as good. If consensus cannot be reached concerning dysplasia or no dysplasia, the dog receives a borderline grade, which allows a resubmission of new radiographs after 6 months. Unaffected dogs receive a specific number and the results are published on the OFA website, which can be freely consulted by the public. Results of CHD-affected dogs are sent to the owner and unless the owner agrees, are not publicly available. Breeders are completely free to choose their breeding dogs, irrespective of OFA scores. This implies that offspring from affected dogs can receive a pedigree.

The Fédération Cynologique Internationale (FCI)

The FCI was founded in 1911 and is a cooperative of different national kennel clubs. The FCI system for screening CHD has been used for 40 years and is currently applied by 84 national members (1/country) in Europe, Russia, South America, South Africa, and Asia.[12] Radiographs should be interpreted and scored by a specialized veterinarian, approved by the national kennel club and/or the breed club in which the dog is registered. In most instances, a single observer per breed club is responsible for scoring radiographs. In reality, the individual breed club selects the observer and a training requirement is not mandatory. The FCI recommends that all of its members, partners, and screening organizations facilitate participation of their members on scoring panels in an official FCI program of equilibration of CHD scoring.

The scoring system combines the subjective standard hip-extended radiographic evaluation with the NA measurement (Fig 1). A frog-leg position radiograph, with the stifles abducted, can be used to optimize scoring, but is not required.[13,14] There are 5 different scores (A–E; Table 1) assigned that represent the severity of disease.[15] Grades A and B are considered nondysplastic whereas grades C–E are considered dysplastic hips. Final scoring is based on the worst of the 2 hip joints. The minimum age for screening is 1 year for most breeds and 18 months for large and giant breeds.

Dogs should be deeply sedated or anaesthetized to achieve complete muscle relaxation.[14] The criteria used to ban a dog from breeding are not clear: some dogs with mild dysplasia can still be used in certain breeding programs. Individual breeding clubs decide whether dogs with CHD may be used. Reports are sent to the owners and publication of results is left to the discretion of the individual breeding organizations. Advice on breeding strategies by the FCI is poor. In some countries and some breeds, offspring from affected parents do not receive a FCI pedigree.

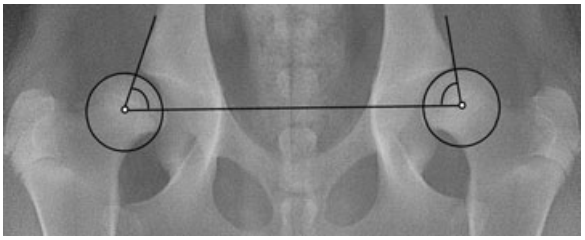

Figure 1 Norberg angle measurement—the angle of the line that connects the femoral head centers and the line from that center to the cranial lateral acetabular margin.

The British Veterinary Association/Kennel Club (BVA/KC)

Since 1965, dogs have been screened for CHD by the "pass" or "fail" BVA/KA system. In Britain, Ireland, and Australia, a numerical scoring system has been used since 1984 with the minimum screening age being 1 year. Standard hip-extended radiographs obtained with dogs deeply sedated or anesthetized, are scored using 9 criteria (score range: 0–6, except for the caudal acetabular edge that is scored 0–5). The right and left hip joints are screened separately and the scores for each hip are summated to obtain the total hip score (range, 0–106; 53 for each hip).[6] Higher scores implicate a worse hip status. The 9 criteria are NA, degree of subluxation (femoral head position related to the dorsal acetabular edge), cranial acetabular edge (in relation to the femoral head), dorsal acetabular edge (degree of curvature and amount of exostosis), cranial effective acetabular rim (degree of sharpness and amount of exostosis), acetabular fossa (amount of visibility and remodeling), cranial acetabular edge (sharpness and amount of exostosis), femoral head and neck exostosis (amount of exostosis and presence of a Morgan line), and femoral head recontouring (degree of fit into a circle, which depends on the amount of exostosis and remodeling).[6]

Scoring of hips is by 2 observers in consensus, recruited from a group of specialist radiologists or surgeons. Only dogs with a score well below the breed mean score (average, 10–20 for both hips) are recommended for breeding. Because each breed has its unique hip joint characteristics and dysplasia frequency, the BVA/KC releases regular updates of breed mean score. Rolling updates are not provided but rather a mean of all dogs screened since the program began. The Kennel Club is responsible for publishing hip dysplasia results for all pedigree dogs in the Kennel Club Breed Records Supplement and on progeny registration certificates.[16] Breeders are not obliged to enroll their breeding dogs into the screening system, which implies that dysplastic dogs can still be used voluntarily.[13]

Comparison of OFA, FCI, and BVA/KC Screening Approaches

Comparison of these grading systems is difficult. There is no gold standard for the diagnosis of CHD and the same hip-extended screening system even differs among countries (FCI). Age at screening and sedation at screening, which significantly affect results, are not standardized between

Table 1 Overview of the Different Grading Systems for Canine Hip Dysplasia, Based on the Standard Hip-Extended Radiographic Projection. Variations on the FCI System Are Applied in Several European Countries.

		FCI		Germany	Netherlands	Switzerland	BVA/KC	OFA
No signs of hip dysplasia	A	NA	A1	Normal	Negative optima forma	Free	0–4 (no > 3/hip)	Excellent
		>105°	A2		Negative not entirely perfect		5–10 (no > 6/hip)	Good
Near normal hip joints	B	NA*	B1	Normal almost normal	Transitional	I	11–18	Fair
		≤105°	B2				19–25	Borderline
Mild hip dysplasia	C	NA	C1	Still acceptable	Mild positive		26–35	Mild
		100°	C2					
Moderate hip dysplasia	D	NA	D1	Moderate	Positive	II	36–50	Moderate
		>90°	D2					
		<100°						
Severe hip dysplasia	E	NA	E1	Severe	Positive	III	51–106	Severe
		<90°	E2		Positive optima forma	IV		

*Norberg angle 105° with slight incongruency or <105° with congruency.
FCI, Fédération Cinologique Internationale; BVA/KC, British Veterinary Association/Kennel Club; OFA, Orthopedic Foundation for Animals; NA, Norberg angle.

screening approaches.[17–24] An attempted comparison of the hip-extended screening approaches is provided in Table 1.

The Pennsylvania Hip Improvement Program (Patented July 1993)

Smith and co-workers developed the PennHIP in 1983, and was commercially introduced in 1994.[25] Currently, the University of Pennsylvania manages PennHIP as a not-for-profit organization.[26] Unlike the 3 traditional screening methods, the PennHIP method mainly focuses on passive hip joint laxity with the objective of detecting passive joint laxity as young as 16 weeks to create a breeding pool of dogs with tighter hip joints in successive generations.[27] To obtain complete accuracy, the recommended age for screening is 6 months. A standard hip-extended radiograph is also included to investigate signs of osteoarthritis.

The anesthetized or deeply sedated dog is positioned in dorsal recumbency and the femurs are held in a 10–15° extension (called the neutral position). The proximal aspect of the femurs is compressed into the acetabulum. This compression view determines the compression index (CI), a measure for hip joint congruency. With a custom made distractor, positioned between both pelvic limbs, the femurs are abducted, allowing a lateral displacement of the femoral head from the acetabulum (Fig 2). A distraction index (DI) is calculated from the radiographs (Figs 3 and 4) and the results reported, quantifying the relative degree of femoral head displacement from the acetabulum. DI ranges from 0 to 1, with 0 representing full congruency of the hip joint and 1 representing complete luxation.

Only PennHIP-certified veterinarians can officially perform the PennHIP procedure and enroll the radiographs into the evaluation procedure at the PennHIP Analysis Center. PennHIP has a mandatory submission policy. After the radiographs are reviewed, a Hip Evaluation Report is mailed to both the veterinarian and the owner, who are informed of the DI of each hip and the grade of DJD (based on the looser of the 2 hips) relative to the other members of its breed. It is not a pass or fail system. Dogs with a DI < 0.3 are considered not to develop DJD in later life, whereas dogs with a DI of ≥ 0.7 are very likely to develop the disease. The chance of developing DJD in later life increases with increasing DI: > 50% of dogs with a DI between 0.3 and 0.7 develop DJD but some uncertainty remains, depending on breed characteristics. DI are breed-specific and are available from the PennHIP database.[26,28] Specific information for breeders of dogs with passive hip laxity is provided.[27]

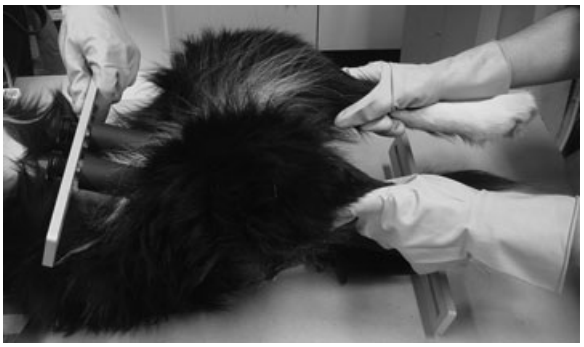

Figure 2 Pennsylvania Hip Improvement Program (PennHIP) position with distractor.

The Dorsolateral Subluxation (DLS) Approach (Patented June 1999)

Since recognition of hip joint laxity as an important trait in the pathogenesis of CHD, laxity has been investigated and standardized. The position of the dogs in the DLS system is described as weight bearing[10] and it is claimed that the DLS method obtains a more functional hip laxity whereas PennHIP generates a passive hip laxity. To determine the DLS, the anesthetized dog is positioned in ventral recumbency on a custom-made foam block with the stifles flexed

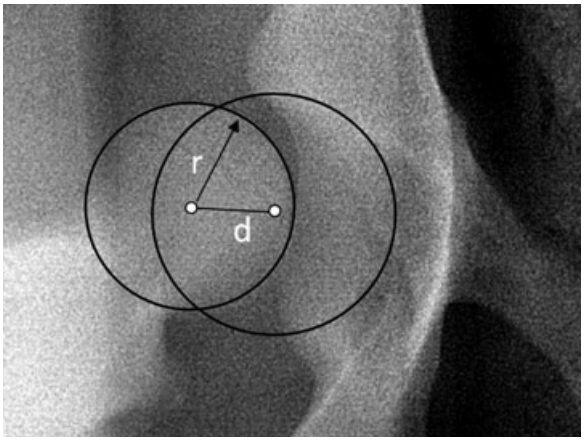

Figure 3 PennHIP distraction index measurement (DI) = d/r. d, distance between the centers of the best fitting circles through the femoral head and the acetabulum; r, radius of the best fitting circle through the femoral head.

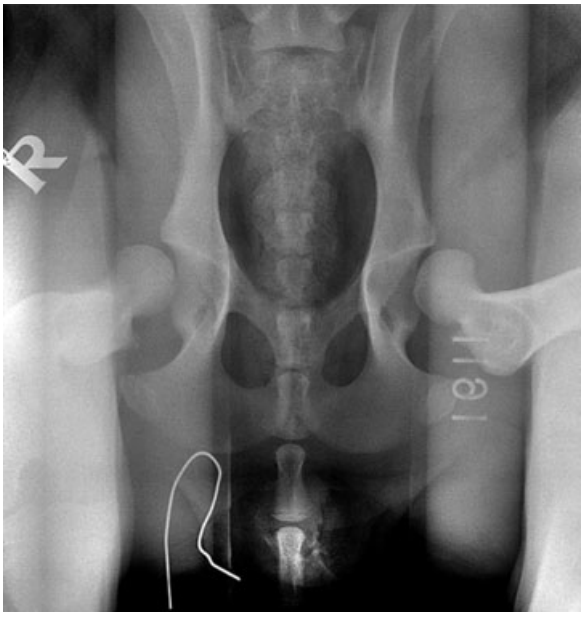

Figure 4 PennHIP: distraction (neutral) view.

into a depression of the block; both femurs are perpendicular to the table top and receive the compressive weight of the animal, stressing the coxofemoral joint (Fig 5).[10] Whether this procedure mimics physiologic loading of the hip joint remains a subject of discussion. On the dorsoventral radiograph (Fig 6), the percentage of femoral head that remains medial to the most lateral aspect of the cranial acetabular rim is calculated (Fig 7) with a high percentage implying a tighter hip. DLS scores did not change after 8 months of age and reasonably predicted cartilage lesions at a later age. Dogs with DLS scores > 55% are unlikely to develop CHD in later life, whereas dogs with a score < 45% have a greater chance of developing CHD.[29] Although not in use in mass

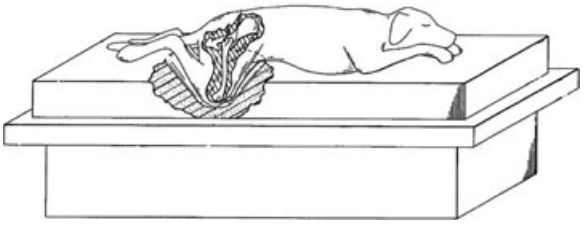

Figure 5 The Dorsolateral Subluxation (DLS) position: the animal is placed in a foam block with the stifles somewhat caudal of the hip joints to avoid radiographic overlapping (Farese JP, Todhunter RJ, Lust G, et al: Dorsolateral subluxation of hip joints in dogs measured in a weight-bearing position with radiography and computed tomography in dogs. *Vet Surg* 1998;27:393–405).

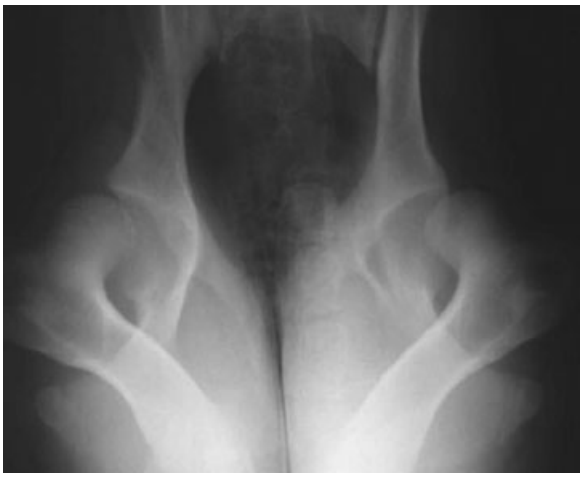

Figure 6 Dorsolateral subluxation radiographic projection (Ginja MMD, Silvestre AM, Gonzalo-Orden JM, et al: Diagnosis, genetic control and preventive management of canine hip dysplasia: a review. *Vet J* 2010;184:269–276).

selection screening programs, the DLS score is one of the traits used in genetic studies. The relationship between the DLS score and the development of DJD over the lifetime of a dog warrants further investigation.

Evaluation of the Different Approaches

Both the OFA and FCI systems rely on a descriptive (qualitative) method to detect DJD and laxity to diagnose CHD, with the exception of the quantitative NA measurement in the FCI system. The BVA/KC and the Swiss scoring mode use a numerical method.[30,31] Evaluating radiographs remains subjective regardless of quantification approaches. Furthermore, extension and internal rotation of the hip joint causes winding-up of the joint capsule, minimizing passive laxity.[8,9,32] The neutral position maximizes hip joint laxity.[33]

Early diagnosis of CHD, which is critical to prevent affected dogs from use in breeding programs, is unreliable because detection of latent DJD is difficult at an early

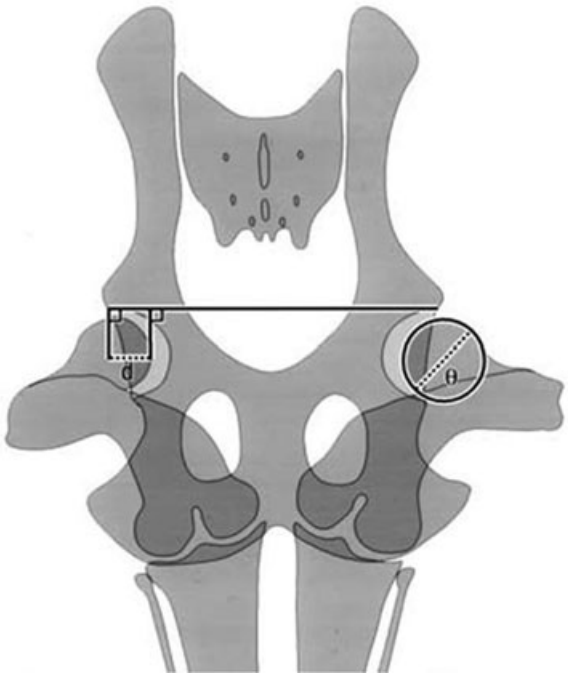

Figure 7 The DLS score (%) is calculated as $d/\theta \times 100$ (d: distance between a line dropped from the cranial acetabular lateral margin and a paralell line, tangential with the most medial surface of femoral head; θ: diameter of the best fitting circle of the femoral head) (Farese JP, Todhunter RJ, Lust G, et al: Dorsolateral subluxation of hip joints in dogs measured in a weight-bearing position with radiography and computed tomography in dogs. *Vet Surg* 1998;27:393–405).

age. Therefore, most CHD control programs require radiographs at 1 year of age and in the United States at 2 years. Re-examinations at older ages (eg, 5 years) to identify false negatives are not required or recommended by any of these organizations. In a study with a lifelong follow-up of a colony of Labrador Retrievers for development of hip DJD using DI and standard hip-extended projections, CHD was expressed linearly over time and can also develop in old age.[34]

Hip laxity, which is considered predictive for the development of DJD and CHD in later life, can be detected as early as 16 weeks of age,[33] which might increase the impact on breeding strategies. Unfortunately, most puppies are sold at 10–12 weeks. Early DI measurement is the most important risk factor for development of hip DJD among all phenotypes tested thus far[28,35,36]; however, the degree of radiographically detectable passive hip joint laxity may not be directly related to the functional pathologic joint laxity necessary for development of degenerative changes associated with CHD.[37] In the same study, dogs with laxity (subluxation) on a preliminary hip extended radiograph were more likely to have normal hip status at 24 months, whereas dogs that had radiographic changes early in life, developed signs of DJD at 24 months.[37] The reported DI at 4 months had a 48% false positive rate and 57% at 6 months when evidence of DJD was identified at 12 months of age.[9] These false positive rates were higher than the OFA method (17.6% and 10.0%, respectively).[37] It was concluded that the OFA test is an appropriate test for early mass screening of hip joint status. However, the risk of occurrence of CHD-related DJD remains throughout a dog's life: the overall prevalence of DJD in a litter of Labrador Retrievers was 15% at 2 years of age and 67% at 14 years, implying that passive hip laxity at an early age may have repercussions at an older age.[34,38]

A strong correlation has been observed between DLS score and DI.[10] This might suggest that, as with the PennHIP method, the DLS method measures passive hip laxity. When the hip-extended method is compared with the DLS score, the latter can be used for earlier (<1 year) detection of CHD-related subluxation.[10] This is in harmony with the PennHIP method.[8,9,25,28,33,35]

Interobserver agreement in the OFA system is reportedly high: 93.4–94.9% for classifications of normal, borderline or an abnormal phenotype.[37,39,40] However, other studies report far lower interobserver agreement of 31–68%.[41] This is in agreement with recent findings for the FCI system where interobserver agreement remains low despite experience and increased radiographic quality.[42–44] Inter- and intraobserver agreement of DI is high ($\rho = 0.85$–0.94) even for nonexperienced examiners.[45] Repeatability of the DLS method is also high ($\rho = 0.87$).[10]

Because the radiographic schemes focus on hip phenotype as an estimate of the genotype, the test value can be expressed in the concept of heritability: by knowing the hip scores of related animals, it is possible to estimate the heritability for CHD or CHD-related traits. Heritability values for CHD or CHD-related traits differ between breeds according to the applied diagnostic test. Heritability estimates vary in different studies from 0.20 to 0.74.[46–48] Furthermore, heritability estimates are difficult to compare because scoring systems differ between countries,[46] although there is a significant correlation ($\rho = 0.74$) between the OFA and BVA/KC systems.[49] In a colony of Labrador Retrievers, estimated heritability of total hip dysplasia grade (FCI system), NA, coverage of the femoral head, craniodorsal acetabular rim, subchondral bone sclerosis, shape of the femoral head and neck, and joint capsule insertion changes were 0.44, 0.43, 0.46, 0.37, 0.32, 0.21, and 0.05, respectively.[50] According to a recent study, estimated heritability for the DI, DLS score, NA and hip-extended radiography in 17 dog breeds are 0.61, 0.54, 0.73, and 0.76, respectively.[51] Unfortunately, not all dogs were measured with all 4 tests, which may have influenced the results. The NA used as a reference for hip joint laxity when analyzing quantitative trait loci (QTL) in Portuguese Water Dogs, was highly heritable ($h^2 = 0.73$).[52]

The NA, with a threshold of 105° for defining the hip as normal on a hip-extended radiograph, was not a reliable predictor of DJD susceptibility in 7 breeds: even in dogs with a NA of 105°, a high percentage of false-positive and false-negative diagnoses were made.[53] On the other hand, when the OFA system, DLS score, DI, and NA were used on

radiographs of 8-month old dogs to predict cartilage lesions at 12 months of age, the combination of 2 systems predicted the development of normal hips and osteoarthritic hips better than when a single system was used. The best predictor was the combination of DLS score and NA.[54] According to Smith, the assumption of cartilage lesions at 12 months as a gold standard for DJD is a shortcoming in that study: in most dogs, DJD manifests itself later in life when the entire lifespan of dogs is considered.[55]

When the NA was measured using computer image analysis versus manual caliper measurement, the reproducibility was doubled, which resulted in a more accurate distinction between dysplasia/nondysplasia and the various FCI grades.[7]

The early finding of a caudolateral curvilinear osteophyte (CCO ; Morgan line) predicted development of DJD and hip dysplasia. In 76% of Labrador Retrievers, it was the 1st radiographic sign and 95% of dogs had histopathologic evidence of osteoarthritis.[56] The presence of a CCO at an early age (6–7 months) was highly predictive for development of CHD at 10–12 months.[57] Dogs with a CCO were 7.9 times more likely to have DJD as were those without CCO, and DI was a risk factor for development of CCO.[58] The circumferential femoral head osteophyte (CFHO) is a radiopaque line that encircles the femoral head at the level of the attachment of the joint capsule and represents an early osteoarthritic marker in dogs with CHD.[57,59] The CFHO tends to occur at a later age (mean, 5.4 years) than CCO. The CFHO has a sensitivity of 100%.[59]

The Effect of Screening on the Prevalence of Canine Hip Dysplasia (CHD)

Analysis of the OFA database between 1972 and 2000 shows a steady decrease in CHD prevalence for most breeds.[40] A steady increase in dogs with an excellent grade and a decrease in dogs with a fair hip score was reported.[40] There was an increase in mild and a decrease in moderate dysplasia. Between 1974 and 1984, prevalence of CHD ranged from 0.6% (Borzoi) and 46.9% (Saint Bernard), which implies a median 22.4% decrease in prevalence compared with screening between 1966 and 1973.[39] A decrease in CHD prevalence in 79% of breeds and an increase of 88% of excellent hips was noted when 1972–1980 and 1981–1988 were compared.[60] These findings are in agreement with studies comparing 1970–1990 and 1989–2003, where a significant increase of excellent and good scores was observed.[61,62] However, these results have to be interpreted with caution because selection bias may have an important impact on database research.[63] For example, during the period between 1970 and 2000, only dogs with excellent, good, or fair hip scores were publicly reported by the OFA. All dogs were simply reported as "normal" until the second half of 1985. Starting from 2001, dysplastic dogs and dogs with borderline scores were reported in the OFA database.[64] Radiographs of normal appearing hips are 8.2 times as likely to be submitted to the OFA, which implies that many radiographs from dogs with abnormal hip appearance are not sent for screening.[65] Therefore, the prevalence of CHD may be much higher than reported in previous studies.

In the PennHIP system, it is mandatory for veterinarians to submit all radiographs without exception; if not, the license to perform PennHIP procedure can be withdrawn, potentially minimizing nonresponse bias.[66] In Finland, all radiographs of dogs that enroll for screening are sent for official screening.[67] In a study carried out in France comparing 1993–1999 and 2000–2006, there was a significant decrease in CHD prevalence in 6 of 31 dog breeds investigated.[68] In Sweden, a 22% decrease in CHD in German Shepherds was noted when comparing a screening period before 1970 and 1975.[48] Another Swedish study demonstrated a decrease in CHD prevalence.[69] A retrospective study of the Finnish Kennel Club's hip dysplasia screening program showed no significant changes in dysplasia prevalence in dogs born from 1988 to 1995 and those born before 1988.[4] The CHD prevalence in a Swiss population of Labrador Retrievers between 1972 and 1980 was 57.9% and decreased to 14.9% between 1991 and 1996.[70] In a study of the BVA/KC program for controlling CHD in 6 breeds between 1987–1990 and 1991–1995, the decrease in prevalence was lower than expected from theoretical models and scores did not show consistent trends in 5 of the 6 breeds.[3] Comparing the prevalence of CHD in German Shepherds, Golden Retrievers, Labrador Retrievers, and Bernese Mountain dogs in Belgium with other countries over several time spans, it was concluded that the Finnish prevalence was 10% higher than those in the United States and Sweden, and that the overall prevalence of CHD remains high.[5] To our knowledge, there are no reports regarding the evolution of prevalence of CHD using the PennHIP or DLS systems.

Screening results (positive or negative) for phenotypic appearance of multifactorial diseases should be available in open registries. The results should be used to aid the selection and combination of breeding dogs. Breeder's participation, which is voluntary in all screening organizations, plays an important role in the eradication of inheritable diseases. Breeder inexperience, low report rates, and selection of breeding based on 1 individual breeding dog, without knowledge of phenotype characteristics of related dogs, are possible reasons for a low impact on desirable or undesirable inheritable traits.

One example to increase the impact of screening on selection of dog breeding is in Sweden, where ~50% of all susceptible breeds are screened annually[68]; 70% of dogs are purebred and registered with the Swedish Kennel Club. Sire and dam must be screened before pups can be registered. In many breeds but not all, only dogs with normal hip status (nondysplastic) are accepted for breeding and the use of dysplastic dogs in breeding is unusual. To get the dogs fully insured, which is the case in about three-quarters of all registered dogs, dogs must be evaluated. All results are distributed to the breeders.[69]

Until now, breeding strategy has been based on mass selection, which focuses on breeding a phenotypically good

sire with a phenotypically good dam. The introduction of breeding values, which represents the genetic quality of a dog for a certain trait, could increase the efficacy of current breeding programs.[4,9,51,64,71–78] Breeding values are based on a mathematical approach to pedigree data. Because it is elusive to know all elements of the pedigree, statistical models are applied to estimate the breeding value (EBV). The most valuable statistic models are the Best Linear Unbiased Prediction (BLUP) and the Restricted Maximum Likelihood (REML).[78]

Genotyping CHD

The most logical approach to eradication of a genetic disease is to detect genetically affected animals, prevent them from breeding, or combine them as such that affected offspring can be prevented where prevalence of the disease is extremely high. The search for genes that are responsible for CHD is complex. Mapping the dog genome using genetic markers has been undertaken.[79,80] Quantitative trait loci analysis is a statistical method that allows identifying complex phenotypic traits to certain locations on chromosomes by the use of marker molecules. Mutations related to hip laxity (DI and DLS) and NA are identified by mapping the 38 autosomes and X chromosome of dysplastic Labrador Retrievers and trait-free Greyhound crossbreed dogs: 12 candidate locations for CHD were found.[81] In the German Shepherd dog, a whole genome scan to detect QTL revealed 19 candidate chromosomes responsible for CHD, with chromosome CFA9 as the strongest possible candidate.[82] Heritability estimates for DLS and DI by use of QTL were 0.6 and 0.5, respectively, with DI as a possible major gene locus.[83] A QTL that contributed to a variance of 16% of osteoarthritis because of CHD was detected in a pedigree of Portuguese Water Dogs.[84] In Labrador Retrievers, the highest QTL was found for NA and DLS for the right hip. The QTLs were found on the same chromosome as reported for Portuguese Water Dogs and German Shepherds.[85]

Fine mapping the dog genome for QTLs is necessary in dysplastic pedigree dogs and in unrelated dogs. The ultimate goal is not only to determine genes responsible for CHD, but also to detect genes that protect dogs from developing CHD. Without prior trait mapping, the genetic search for complex diseases such as CHD was not successful in affected dogs.[86] High-quality draft genome sequencing of the dog genome together with mapping of single nucleotide polymorphisms (SNPs) across breeds has been performed.[87] Because selective breeding has led to large haplotype blocks being carried into the canine genomes, fewer markers are required to identify genetic disease associations. With this knowledge, a genetic test (CanineHD Genotyping Bead Chip, Illumina SNP Genotyping®, San Diego, CA) has been introduced. It allows genotyping the dog's susceptibility for CHD with a set of markers. Although the technique is promising, scientific validation is still to be performed. In a simulation model of German Shepherd dogs, higher selection response than in the exclusion cases was achieved by selecting on the genomic breeding value and CHD score. In this hypothetical model, genomic selection would be the method of choice in the future.[88] Friedenberg et al identified the first gene that expresses all 4 traits of radiographic CHD (NA, DLS, DI, and OA according to the OFA hip-extended radiographs): the fibrillin 2 gene (FBN2) on chromosome 11 (CFA11) of affected Labrador Retrievers and other breeds. FBN2 codes for a glycoprotein (microfibril), which is expelled from fibroblasts and chondrocytes into the extracellular matrix, where it regulates the expression of elastin and of transforming growth factor beta (TGF-β). Elastin quality determines the elastic properties of connective tissues, such as ligaments and joint capsules whereas TGF-β regulates the growth and repair of tissues. TGF-β has a direct and indirect effect on surrounding cells and on the integrity of the extracellular matrix. A mutation in FBN2 downregulates gene expression, causing excessive deposit of erroneous elastin and local increase of TGF-β expression. Unfortunately, the mechanism between altered FBN2 expression and the development of CHD remains unclear.[89] The goal of genotyping is the introduction of Real Breeding Values, which represents the actual genetic quality of the dog based on causal gene information and not on phenotype information.

Conflicting data about agreement, concordance between systems, heritability estimates, and the effect on prevalence of radiographic methods confuse breeders, owners, and veterinarians. This will inevitably have a negative impact on efforts to combat CHD. Additionally, all screening mechanisms should uniformly advise breeders on breeding protocols. Existing breeding protocols should focus more on population genetic control mechanisms for each breed. As long as dysplastic dogs are used for breeding, a small amount of biased offspring is tested and phenotypically normal but genotypically poor dogs are used for breeding, no lasting reduction in CHD prevalence will be achieved. The unraveling of the canine genome, with the detection of genes responsible for CHD is promising. However, current data on genome analysis demonstrate a large grey zone of uncertainty for the risk of a dog being CHD affected, similar to the uncertainty noted with the DI and all other methods.[90]

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