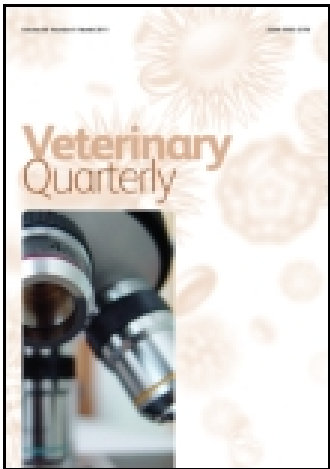




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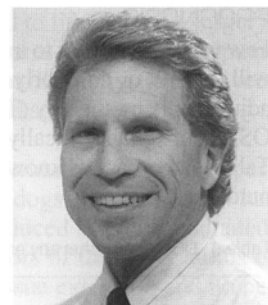
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CANINE HIP DYSPLASIA: PATHOGENESIS, DIAGNOSIS, AND GENETIC CONTROL

G.K. Smith¹



Orthopedic Surgery & Dentistry

CANINE HIP DYSPLASIA: PATHOGENESIS AND DIAGNOSIS

Canine hip dysplasia (CHD) is the most common orthopedic disease in large and giant-breed dogs. Although our understanding of CHD has evolved over the years, progress has often been more a result of clinical empiricism than well-conceived scientific investigation. Canine hip dysplasia continues to be a source of considerable debate, controversy, and conjecture among veterinarians, dog breeders, and dog owners. The controversy notwithstanding, it is generally accepted that hip laxity plays an important role in CHD.

Olsson in 1966 defined hip dysplasia as a 'a varying degree of laxity of the hip joint permitting subluxation during early life, giving rise to varying degrees of shallow acetabulum and flattening of the femoral head, [and] finally inevitably leading to osteoarthritis (1). It is this empirical association between hip laxity and degenerative joint disease (DJD) that has formed the basis for hip dysplasia diagnostic scoring systems worldwide.

A tentative diagnosis of canine hip dysplasia (CHD) can be gleaned from the history, clinical signs and results of hip palpation. A definitive diagnosis, however, by convention, is made only if characteristic signs of CHD are evident on a ventrodorsal radiograph of the pelvis. Radiography is performed with the dog, preferably sedated, in dorsal recumbency, its legs fully extended, and its stifles internally rotated. This radiographic position was adopted as the standard in the USA more than 35 years ago. Scoring of the radiograph varies by country, however, most scoring systems utilize a subjective or qualitative assessment of hip phenotype in arriving at a diagnosis of CHD. In most scoring systems a diagnosis of CHD is made if there is radiographic evidence of either hip joint subluxation (laxity), or DJD or both. Radiographic evidence of DJD usually includes one or more of the following: femoral periarticular osteophyte formation, subchondral sclerosis of the craniodorsal acetabulum, osteophytes on the cranial or caudal acetabular margin, or joint remodeling from chronic wear.

The principal reason hip dysplasia is a concern to dog owners, dog breeders and veterinarians is that the associated hip DJD can cause discomfort and disability. Although CHD has an extremely high prevalence, thankfully it is a kind disease, in that the vast majority of dogs with CHD show no

overt clinical signs until perhaps in their geriatric years. Dogs are born with normal hips and if predisposed to CHD develop radiographic evidence of laxity after two months of age and DJD usually some time after four to six months of age and often much later. It is this latent development of the characteristic disease phenotype that makes early diagnosis of CHD unreliable (16% accurate at six months of age) (2). This realization has prompted most subjective hip scoring schemes to begin at one year of age at the very earliest. In the USA dogs are not certified to be CHD-free until two years of age.

The latent development of radiographic signs of CHD negatively impacts the reliability of subjective hip scoring. Problems with reliability also arise from variation in diagnosis among radiologists. Few scientific studies have been undertaken to assess either the magnitude or the effect of this variation on accuracy of hip scoring or on the selection of breeding candidates. The effect of diagnostic variation (error) in determination of a disease phenotype is to lower the estimate of heritability of the phenotypic trait. Low heritability in turn equates to slow rate of genetic change to improve hip phenotype in response to application of selection pressure, e.g., breeding normal to normal dogs. Indeed, data from the University of Pennsylvania have documented a disturbing amount of variation among board-certified radiologists in subjective scoring for hip dysplasia (Kappa values ranged from 0.04-0.20) (3).

The true prevalence of CHD by breed in the general population is unknown. Most hip registries worldwide specify voluntary hip-film submission and understandably only the best hip films are submitted for evaluation. This trend results in a bias that understates the true prevalence of CHD. Our data would suggest that this bias is both large and varies by breed (4). For example, a random sample of subjectively scored hip radiographs from 200 golden retrievers and 132 rottweilers showed the prevalence of CHD to be 74% and 69%, respectively. These figures are two to three times higher than comparable figures reported in the USA by the Orthopedic Foundation for Animals (OFA).

The stress-radiographic method (that has come to be called PennHIP) was developed, at least in part, because of recognized variations among radiologists in regard to subjective hip scores assigned to radiographs (3). Also it was understood that the prevalence of CHD among many dog breeds was disturbingly high, despite efforts to lower prevalence using subjective hip score as a selection criterion (4).

The PennHIP stress-radiographic method was originally designed in 1983 to explore the precise relationship between passive hip laxity and the ultimate development of DJD. Hitherto, this relationship was empirical. The PennHIP method of hip evaluation requires that dogs be se-

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dated or anesthetized and positioned in dorsal recumbency (5). A standard, ventrodorsal, hip-extended radiographic projection is the first of three radiographs to be made. Two additional radiographs are obtained with the hip joints in the neutral position: a compression view with the femoral heads fully seated in the acetabula and a distraction view with the femoral heads displaced laterally by use of a custom-designed device placed between the legs that acts as a fulcrum on the femur at the level of the ventral aspect of the pelvis. The relative degree of femoral head displacement from the acetabulum is quantitated by calculating a distraction index (DI). The DI ranges from zero to > one, with zero representing full congruency of the hip joint and one representing complete luxation. The standard, ventrodorsal, hip-extended radiographic projection is included as part of the PennHIP analysis to permit subjective grading for the presence of DJD. This subjective grade is combined with the quantitative DI to determine on a population basis the breed-specific relationship of passive hip laxity to the development of DJD (6,7,8).

The DI method was developed on the basis of results of mechanical testing of cadaver hips, which accomplished three principal objectives. First it showed that when the hip is in the standard hip-extended, internally rotated position, passive laxity is minimized (5,9,10). Second, it showed that passive laxity was maximized when the hip is in the neutral position (9). Third, it demonstrated the sigmoidal nature of the load/displacement curve for the hip joint in the neutral position, which suggested that high repeatability from examiner to examiner in regard to measured DI could be expected without the need to standardize applied force (10). The mean and range of DI was shown to vary from one breed to the next, but within an individual dog, hip laxity as measured by the distraction index appears to remain constant (within limits of scientific acceptability and clinical applicability) from 16 weeks of age (6). Passive laxity measured on the distraction radiograph is on average 2.5-11 times greater than that measured from the standard, hip-extended radiograph (5). Performance borzois and greyhounds which have an extremely low prevalence of CHD have tight hips ($DI < 0.3$) (5) and mean DI for breeds of dogs that have a high prevalence of CHD is significantly greater than mean DI for borzois and greyhounds (5). However, individual dogs that have $DI < 0.3$ even though members of breeds prone to CHD, have a low risk of developing DJD. Some, but not all, dogs with $DI > 0.3$ will develop DJD by three years of age, and DI has been shown to be the most important risk factor for development of hip DJD (6-8). Susceptibility to development of DJD appears to be breed-specific. For example, given equivalent DI, German shepherd dogs are more at risk for developing DJD than are rottweilers (8). Heritability of DI is higher than that of the subjective hip score (12). Selection pressure based on DI should result in faster genetic change than selection pressure based on subjective hip scores. Finally, the DI method has been performed on approximately 16,000 dogs, some of which were evaluated multiple times. It is apparent that this method is no more harmful than the standard hip-extended radiographic method or palpation performed as part of a routine orthopedic examination (13).

GENETIC CONTROL OF CANINE HIP DYSPLASIA

Controlling polygenic diseases like CHD requires a concerted and coordinated effort on the part of breeders and vet-

erinarians. As importantly, the integrity of the test used to diagnose CHD is central to reducing the frequency of hip disease (figure 1). The principal objective of selective breeding is to maximize the pairing of good genes by breeding dogs not overtly affected with or susceptible to CHD (figure 2). The diagnostic test evaluates hip phenotype as an estimate of the genotype. The relationship between phenotype and genotype is embodied in the concept of heritability represented as the symbol, h^2 . Heritability is defined as the ratio of additive genetic variation (V_G) to the overall phenotypic variation (V_P) of a given trait ($h^2 = V_G/V_P$). Environmental factors (sometimes called nongenetic factors), such as diagnostic error, that increase the variance components in the denominator of this relationship, V_P , have the effect of lowering the estimates of heritability. By definition, polygenic traits are influenced by both environmental and genetic effects. For example, a dog's weight is partly influenced by environmental factors in terms of how much it is fed and how much exercise it gets. It is known also that body weight is influenced by genetic effects, i.e., obese parents tend to have obese offspring.

Worldwide the predominant mode of choosing breeding candidates is to make selections based on the individual animal's phenotype, i.e., progeny testing or breeding values, though providing more accurate selection, are not widely used. This practice makes a knowledge of heritability extremely important. Why is heritability so important? Because for a quantitative trait the rate of expected genetic change in the next generation (ΔG) from mating a dog and a bitch is equal to the heritability (h^2) times the selection pressure (how much the parents deviate from the population average for that trait, see equation 1).

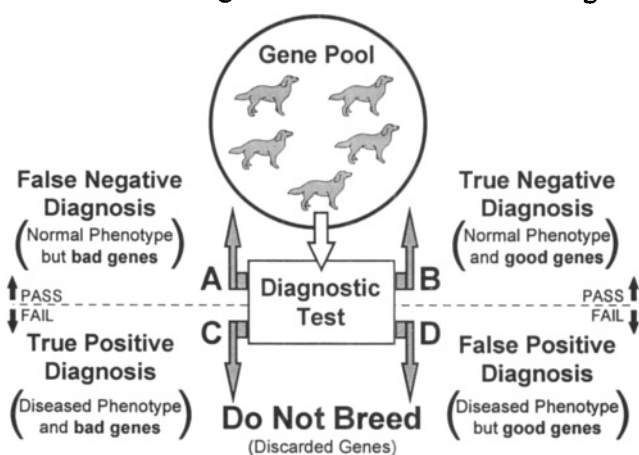
$$\Delta G = h^2 \times (\text{Avg}_{\text{Parents}} - \text{Avg}_{\text{Population}}) \quad (1)$$

Where:

$\Delta G =$	the expected change in average litter phenotype after one generation
$h^2 =$	heritability of phenotype, eg. DI or subjective hip score
$\text{Avg}_{\text{Parents}} =$	average hip phenotype of the parents
$\text{Avg}_{\text{Population}} =$	average hip phenotype of the population from which parents were derived.

Therefore the higher the heritability of a specific trait and the greater the selection pressure applied, the more rapid the expected genetic change per generation of breeding. Unfortunately, few studies of the heritability of subjective hip scores have been published. A thorough literature search could find no published estimates of the heritability of the hip phenotype that is the basis of OFA scoring. However, in 2 well executed studies of subjective hip score similar to that of the OFA, heritability was 0.22¹⁴ and 0.43¹⁵ for German shepherd dogs. For a given phenotypic trait, heritability estimates are population parameters and vary with the population studied. The cited estimates were calculated for particular populations of German shepherd dogs more than 15 years ago when, presumably, variation in disease phenotype was greater than it is today. Years of selection would have been expected to narrow the current range of hip phenotype making present-day estimates of heritability even lower.¹⁶ With decreasing variation in the

Role of the Diagnostic Test in Selective Breeding



The role of a diagnostic test in improving the gene pool. The objective of any genetic diagnostic test is to lower the frequency of 'bad genes' in the gene pool. This entails using what can be seen as a result of the diagnostic test (the phenotype) to estimate what can not be seen (the genes). Dogs are permitted to enter the gene pool based on normal results of the test (arrow A or B). A perfect test (arrow B and C only) would be capable of accurately separating 'good genes' from 'bad genes' on the basis of the phenotype alone (i.e., the test result), thereby quickly and effectively ridding the gene pool of bad genes (arrow B – good genes enter the gene pool; arrow C – bad genes are not recycled). Unfortunately, no diagnostic test is 100% accurate. For example, a test result may wrongly exclude from breeding a dog that tests as having a diseased phenotype even though it harbors good genes (arrow D). This would be an unfortunate missed opportunity, as some good genes would not reenter the gene pool, however, this mistake would not appreciably harm the gene pool. Of greatest potential damage to the gene pool is a test result indicating that a dog has a normal phenotype even though it harbors many bad genes (arrow A). Such a mistake would recycle bad genes through the gene pool, resulting in a steady-state level of disease in the offspring derived from that gene pool, despite the best efforts at selection (e.g., breeding normal to normal). The frequency of disease coming from the gene pool will depend on the sensitivity of the test to detect bad genes. This sensitivity is directly related to the heritability of the phenotype used for screening; therefore the higher the heritability, the better the test.

phenotype (i.e., subjective score) in response to selection pressure, there may come a point at which little additional incremental selection pressure can be applied. That is, if the application of maximum selection pressure (e.g., breeding excellent to excellent, see arrow A in figure) still produces affected progeny, no more genetic progress can be expected (short of incorporating breeding values in making selection decisions). Such has been the experience of The Seeing Eye, Inc. after 17 years of selection against hip dysplasia using a subjective scoring scheme similar to, but more strict than, that of the OFA (12).

Heritability of a given phenotypic trait is a property of the population under study. Therefore heritability of each trait or diagnostic phenotype must be calculated for each breed and each population of dogs. How does one estimate heritability? The upper limit for heritability of DI can be estimated as the intraclass correlation coefficient for longitudinal repeatability of hip score, e.g., DI measurements, over time (16). In 1 study of German shepherd dogs, the intraclass correlation coefficient of repeatability of DI was between 0.67 and 0.74, suggesting high heritability of DI (6). In the same study the longitudinal repeatability of subjective score over the same interval from 4 months of age to 24 months of age was a much lower 0.08 and not statistically significant. Heritability can also be estimated by analyzing resemblance in DI of parents and offspring. To accomplish this, a regression analysis of litter mean DI is

plotted against parent mean DI. Unpublished estimates of heritability of DI for a group of German shepherd dogs was between 0.42 and 0.65, and the upper limit for heritability of DI among a group of labrador retrievers was 0.92.

The most valid estimates of heritability of DI or subjective hip score are derived from analyses of the full pedigree. The Seeing Eye, Inc. has maintained a closed colony of dogs intended for use as dog guides for the blind. Using a derivative-free, restricted maximum likelihood procedure that incorporates the full pedigree structure, Leighton *et al* found the heritability of DI to be 0.46 for German shepherd dogs and 0.46 for labrador retrievers (12). The corresponding heritability estimates for subjective hip score as determined by a board-certified veterinary radiologist were considerably lower: 0.34 for German shepherd dogs and 0.34 for labrador retrievers. Heritability analyses are ongoing for other populations and breeds of dogs, however, early results are promising that the heritability of DI will be considerably higher than the heritability of subjective scoring. When DI is used as a selection criterion, higher heritability equates to more rapid progress in reducing the incidence and severity of CHD in progeny.

Breeders cannot influence heritability, but they can control the magnitude of applied selection pressure (how different the mean of the parents is from the mean of the population at large, see relationship 1). Therefore, to the extent that breeders select breeding candidates, they can control how rapidly improvement can be made in hip phenotype in each generation. For the most rapid genetic change, the breeder can decide to mate only the tightest-hipped dogs within the breed (those with the lowest DI) and then continue to inbreed for tight hips. This approach would maximize the difference between the parent average and population average (i.e., the selection pressure the second term on the right side of relationship 1 would be large). There would therefore be a greater expected change in each generation assuming constant heritability. This approach, however, creates concern that founding a breeding program on only a few dogs, and inbreeding on these dogs, would reduce the overall genetic diversity in the gene pool and could contribute to the loss of some desirable traits or the introduction of some undesirable traits.

To avoid the problems associated with inbreeding and extreme selection, a moderate approach may be more appropriate, particularly in breeds with few members having tight, DJD-unsusceptible hips. In such breeds it may make more sense to choose breeding stock from the tightest half of the breed, thereby maintaining an acceptable level of genetic diversity while still applying meaningful selection pressure. The PennHIP database ranks each dog relative to other members of the breed making it easy for the breeder to identify dogs whose DI will apply meaningful selection pressure. By applying at least moderate selection pressure, eventually the average of the population will shift with each generation toward tighter hips and consequently, fewer dogs will be at risk for developing DJD.

In summary, the heritability of the phenotype measured using the PennHIP method (approximately 0.50 or greater) has been shown to be higher than the heritability of subjective hip score for breeds thus far studied. Such information holds great promise for breeders who, by applying selection pressure based on the PennHIP phenotype, desire to make rapid genetic change toward reducing the frequency and severity of DJD in future generations of dogs.