



CE

Article #2 (1.5 contact hours)

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KEY FACTS

- Presently, breeding animals are chosen based on individual animals (mass selection), leading to slow genetic change.
- To effectively reduce the incidence of canine hip dysplasia, the hip phenotype screening test must have heritability values that are significant enough to lead to genetic change when applied.
- A moderate selection process for tight hips should be chosen by breeders to avoid the problems of inbreeding and extreme selection.

Genetic Control of Canine Hip Dysplasia

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ABSTRACT: Selective breeding of unaffected animals is the only effective means of controlling the frequency and severity of canine hip dysplasia. Genetic control of canine hip dysplasia requires (1) an accurate diagnostic method keyed to a phenotype with optimal heritability, (2) an organized screening program based on the diagnostic phenotype, (3) a centralized database containing essential phenotypic and pedigree information, and (4) trust and cooperation between breeders and the veterinarians who conduct the diagnostic procedure.

Controlling polygenic diseases such as canine hip dysplasia (CHD) requires a concerted and coordinated effort on the part of breeders and veterinarians. As important, the integrity of the test used to diagnose CHD is central to reducing the frequency of hip disease (Figure 1).

THE RELATIONSHIP BETWEEN PHENOTYPE AND GENOTYPE

The principal objective of selective breeding is to maximize the pairing of good genes by breeding dogs not overtly affected with (and preferably, not susceptible to) CHD. 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 by the symbol h^2 . Heritability denotes the reliability of the phenotype in predicting the genotype. A high heritability (e.g., approaching 1) means that the phenotype accurately reflects the genotype. In other words, all the variation in the phenotype is explained by the genes, and no environmental component exists.

Heritability is mathematically defined as the ratio of additive genetic variation:the overall phenotypic variation of a given trait ($h^2 = V_G/V_P$). Environmental factors (sometimes called nongenetic factors), such as diet or diagnostic error, increase the variance components in the denominator of this relationship (V_P); therefore, they have the effect of lowering 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 that body weight can also be influenced by genetic factors (i.e., obese parents tend to have obese offspring).

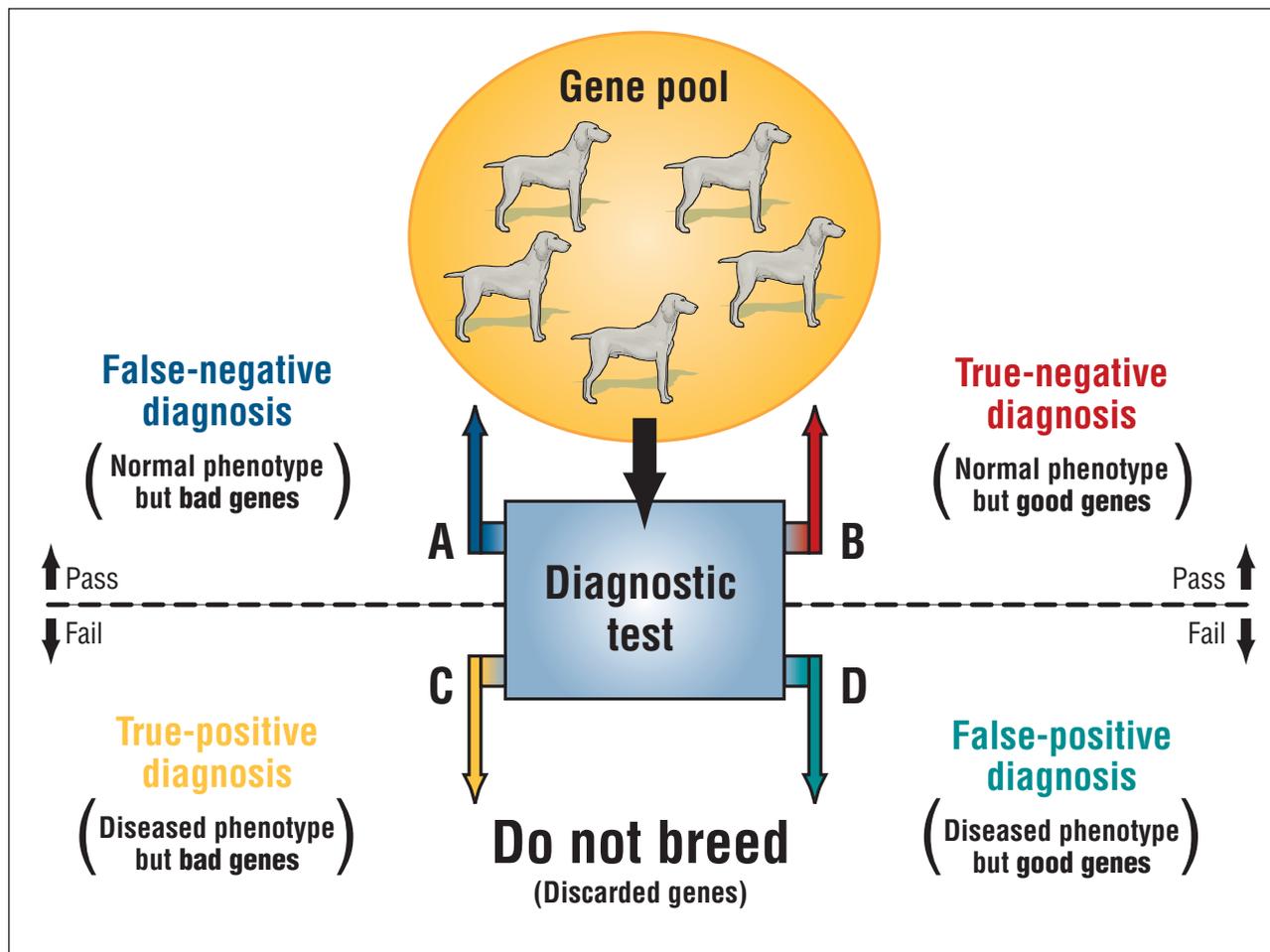


Figure 1—The objective of any diagnostic test for genetic disease is to lower the frequency of “bad genes” in the gene pool. This entails using the results of the genetic test, the phenotype, to estimate the genotype. Dogs are permitted to enter the gene pool based on normal results of the test (*arrow A or B*). A perfect test (*arrows B and C only*) would be capable of accurately separating “good” from “bad” genes on the basis of the phenotype alone (i.e., the test result). This quickly and effectively rids the gene pool of bad genes (*arrow B* indicates that good genes enter the gene pool; *arrow C* indicates that bad genes are not returned). Unfortunately, no diagnostic test is 100% accurate. For example, a test result may wrongly exclude from breeding a dog that tests positive for a diseased phenotype even though it harbors good genes (*arrow D*). This would be an unfortunate missed opportunity because some good genes would not reenter the gene pool; however, this mistake would not appreciably harm the gene pool. The greatest potential damage to the gene pool is a test result indicating that a dog has a normal phenotype (negative) but, in fact, 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 excellent to excellent). The frequency of disease coming from the gene pool depends 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 and the more rapid the genetic change will be.

HERITABILITY

The predominant mode of choosing breeding stock is to make selections based on the individual animal’s hip phenotype, or mass selection. It must be emphasized, however, that this is not the most effective method to select breeding candidates. More rapid genetic change can be accomplished if the hip phenotypes of relatives are incorporated into the selection decisions. By incorporating data from relatives, one can calculate breeding val-

ues for each individual dog. Although this method facilitates more accurate selection decisions, it is not widely employed because of the need for extensive record keeping coordinated with pedigree information. The common practice of selecting breeders by using only the individual animal’s phenotype makes knowledge of the magnitude of heritability of utmost importance.

Why is heritability so important in this regard? Because, for a quantitative trait, the rate of expected

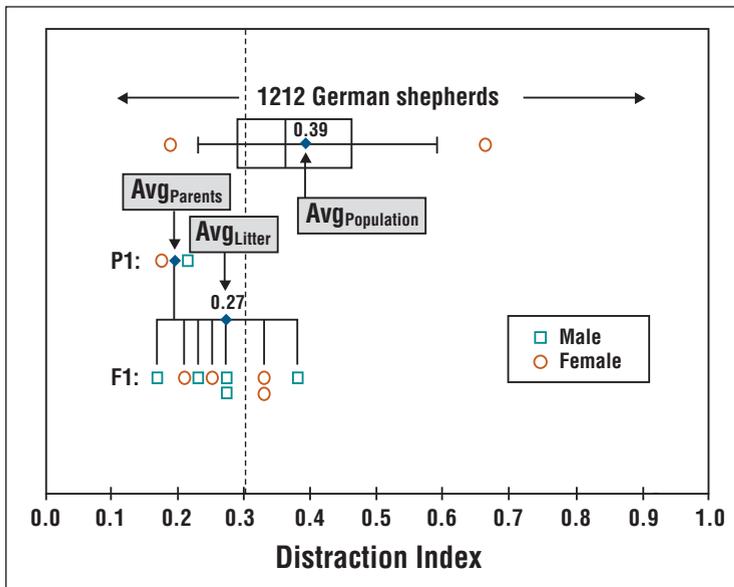


Figure 2—Box plot of the calculation of realized heritability from a single mating. This illustration shows the relative relationships of passive hip laxity of the German shepherd breed at large, of the dog and bitch (*P1*) and of the litter (*F1*). Note that the mean litter distraction index (DI) moved approximately 60% of the distance from the mean of the German shepherd population toward the mean of the parents. Plugging these averages in hip laxity into Relationship 1 yields a realized heritability of approximately 0.6. It is notable that all nine puppies showed hip laxity below the average for the breed and that hip laxity in six of the nine puppies fell below a DI of 0.3, indicating little to no susceptibility to degenerative joint disease.

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 (See Relationship 1 in box). Selection pressure is defined as the deviation of the parental mean hip laxity from the population mean.¹

Therefore, the higher the heritability of a specific trait

Formula for Relationship 1

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

In which:

ΔG = The expected change in average litter phenotype after one generation

h^2 = Heritability of phenotype (e.g., distraction index [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 the parents were derived

and the greater the selection pressure applied, the more rapid the expected genetic change per generation of breeding. These concepts are illustrated in the actual mating of two tight-hipped German shepherds (Figure 2). In this example, extreme selection pressure is applied because the sire and dam are drawn from the tightest 5th percentile of the breed. From the formula above, it is possible to calculate the “realized heritability” of DI. The German shepherd dog population average DI was 0.39 and the parental average DI was 0.2; therefore, the selection pressure applied was 0.19 DI units. The average DI for the nine puppies born to these two parents was 0.27. Therefore, the realized heritability from this single mating can be found by rearranging terms in Relationship 1:

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

When plugging in data from the mating in Figure 2:

$$h^2 = (0.39 - 0.27) \div (0.39 - 0.20) = 0.63$$

Currently, there are no published estimates of heritability of subjective hip scores (the Orthopedic Foundation for Animals [OFA] scoring method) for the most popular breeds of dogs. In two well-executed studies of subjective hip score or OFA-type scoring, estimates of heritability were 0.22² and 0.43³ for German shepherds. A recent retrospective analysis from the OFA found heritability in four less common dog breeds (i.e., English setters, Portuguese water dogs, Chinese shar-peis, and Bernese mountain dogs) to average 0.26.⁴ Phenotypes with heritability of this magnitude would be considered by most geneticists to be lowly heritable,¹ meaning that genetic change will be slow (only 25% of selection pressure will be passed on in each generation of breeding; see Formula for Relationship 1).

Moreover, if selection proves successful, the effect on subsequent generations would be to decrease the overall phenotypic and genotypic variance. With decreasing variation in the hip phenotype (e.g., in subjective score) in the response to selection pressure, there may come a point (a steady state) at which little additional incremental selection pressure can be applied by using the subjective score as a selection criterion. That is, if the application of maximum selection pressure (e.g., breeding “excellent” to “excellent”; see *arrow A* in Figure 1) still produces affected progeny, no more genetic progress can be expected (short of incorporating estimated breeding values in making selection decisions, as mentioned previously). This has been the experience of The Seeing Eye,

Inc. (Morristown, NJ) after 17 years of selection against CHD using a subjective scoring scheme similar to—but more strict than—that of the OFA.⁵

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. An example of a calculation of realized heritability is illustrated in Figure 2; however, estimates of heritability can also be calculated by other methods. For example, 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).¹ In one study of German shepherds, the intraclass correlation coefficient of repeatability of DI was between 0.67 and 0.74, indicating a high upper limit of heritability for DI and in line with the realized heritability calculated above.⁶ In comparison, in the same study the longitudinal repeatability of subjective score over the same interval from 4 to 24 months of age was 0.08 and not statistically significant.

Heritability can also be estimated by analyzing resemblance between parents and offspring in terms of hip laxity (DI). To accomplish this, a regression analysis of litter mean DI phenotype can be plotted against parent mean DI to yield a line; this line's slope is an estimate of the heritability. This method was used by the OFA in a recent publication of heritability estimates.⁴ Using this method, unpublished estimates of heritability of DI for a group of German shepherds was between 0.42 and 0.65, and the upper limit for heritability of DI among a group of Labrador retrievers was 0.92. For golden retrievers, the estimate for heritability of hip laxity from an analysis of 265 dogs comprising 47 litters was 0.64.⁷ For comparison, the estimate of heritability for subjective hip score (slope of regression line) in the golden retriever study was 0.22 and not statistically significant.

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 sophisticated mathematical procedures that incorporate the full pedigree structure, Leighton and colleagues⁸ found the heritability of DI to be 0.46 for German shepherds and 0.46 for Labrador retrievers. The corresponding heritability estimates for subjective hip score determined by a board-certified veterinary radiologist were lower at 0.34 for German shepherds and 0.34 for Labrador retrievers. This low heritability of subjective hip score in German shepherds is supported by a recent study from Finland by Leppanen and colleagues.⁹ Applying best linear unbiased prediction procedures to analyze 10,335 German shepherds

from 1985 to 1997, these investigators found no genetic improvement by using subjective hip score as a selection criterion. Heritability analyses using these more sophisticated methods 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 hip scoring. When DI is used as a selection criterion, the higher heritability equates to more rapid progress in reducing the incidence and severity of CHD in progeny. Currently, there are no published estimates of the heritability of other diagnostic hip phenotypes, including the dorsolateral subluxation score¹⁰; the dorsal acetabular rim score¹¹; and the scores of Fluckiger,¹² Barlow, Bardens, or Ortolani tests. Such studies are necessary to determine the relative merit of these diagnostic tests as candidate hip-screening methods for selecting breeding stock.

SELECTION PRESSURE AND STRATEGY FOR RAPID GENETIC CHANGE

Breeders cannot influence the magnitude of the heritability of the phenotype, but they can control the magnitude of applied selection pressure (i.e., the difference between the mean of the parents and the mean of the population at large; see Relationship 1). Therefore, to the extent that breeders select breeding candidates, they can control the rate of improvement 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 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 may contribute to the loss of some desirable traits or the expression of some undesirable traits. Requiring breeding candidates to come from this small pool would not only seriously reduce genetic diversity, but it would be unacceptable to breeders.

To avoid the potential problems associated with inbreeding and extreme selection, a moderate approach has been suggested in conjunction with PennHIP® testing, particularly in breeds with few or no members having tight (degenerative joint disease–unsusceptible) hips. In such breeds, it is more palatable if breeders are free to choose breeding stock from the tightest half of the breed, thereby maintaining an acceptable level of

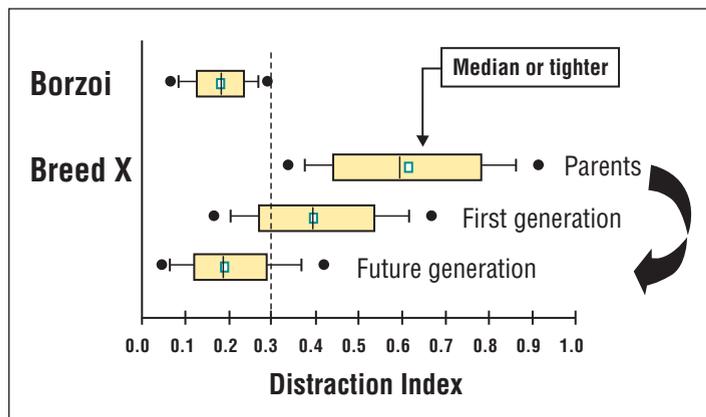


Figure 3—Box plot of proposed minimum laxity-based breeding criteria. By using the generational median (or mean) as the minimal criterion for breeding, genetic change can be expected to occur. Breed X displays a range and distribution of hip laxity not unlike the golden retriever breed. Genetic change toward tighter hips can be expected in each subsequent generation by breeding dogs in the tighter half of the distribution (and preferably much tighter). The goal of this strategy is to tighten the hips of Breed X until they match the range and distribution of hip laxity of the Borzoi. Obviously, based on Relationship 1, the tighter the parent hips, the greater the selection pressure and the more quickly this genetic change toward hip improvement will occur.

genetic diversity while still applying meaningful selection pressure (Figure 3). The PennHIP® database ranks each dog relative to other members of the breed, thereby making it possible 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, increasingly tightening the minimum standard for breeding. Consequently, fewer dogs will be at risk for developing degenerative joint disease. Understandably, more rapid genetic change could be achieved by imposing greater selection pressure or by using estimates of breeding value from incorporation of the pedigree. These strategies are recommended for the aggressive breeder wishing to achieve the most rapid hip improvement. Even without these measures, however, the principle of mass selection—if linked to a highly heritable phenotype, such as the PennHIP® DI—holds great promise for reducing the frequency and severity of degenerative joint disease in future generations of dogs.

CONCLUSION

Finding a magic surgery or medical treatment that will prevent or stop CHD is highly unlikely. Therefore, active genetic controls that use diagnostic tests with high heritability indexes are the best tools in achieving genetic change for CHD. Other measures, such as evi-

dence-based medicine (for making treatment decisions), and modulating environmental factors will help clinicians manage CHD and decrease the disease to acceptable levels.

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ARTICLE #2 CE TEST

The article you have read qualifies for 1.5 contact hours of Continuing Education Credit from the Auburn University College of Veterinary Medicine. Choose the best answer to each of the following questions; then mark your answers on the postage-paid envelope inserted in *Compendium*.

1. Which statement regarding heritability is false?
 - a. Environmental factors decrease the phenotypic variance (V_p) in the calculation of heritability.
 - b. Heritability denotes the reliability of the phenotype in predicting genotypes.
 - c. Heritability is defined as the ratio of additive

- genetic variation:the overall phenotypic variation of a given trait.
- d. Low heritability means that the phenotype does not accurately reflect the genotype.
2. Which statement regarding heritability is true?
 - a. Heritability of a given phenotypic trait is constant for all canine breeds.
 - b. Heritability of passive hip laxity cannot be estimated by analyzing resemblance between parents and offspring.
 - c. The frequency distribution of passive hip laxity is similar for all canine breeds.
 - d. The most valid estimates of heritability of DI are derived from analysis of the full pedigree.
 3. Breeders
 - a. can influence the magnitude of the heritability of a phenotype.
 - b. cannot control the magnitude of applied selection pressure.
 - c. can control the rate of genetic improvement in each generation.
 - d. should never inbreed dogs.
 4. Which of the following is not associated with inbreeding?
 - a. reduced genetic diversity
 - b. slowing the ability to make a genetic change
 - c. loss of desirable traits
 - d. expression of undesirable traits
 5. Which factor does not help control a polygenic disease such as CHD?
 - a. mating young dogs based on presumed phenotypic superiority
 - b. breeder compliance
 - c. veterinary competence
 - d. adequately high heritability index of the phenotype used to diagnose CHD
 6. Optimal selection of breeding stock to reduce the prevalence of CHD should be based on
 - a. gait.
 - b. muscular development.
 - c. hip phenotypes of the breeding candidates.
 - d. hip phenotypes of the breeding candidates and relatives.
 7. Subjective hip score
 - a. reduced to zero the incidence of CHD in dogs bred by The Seeing Eye, Inc.
 - b. demonstrated no genetic improvement in hip quality when used as a selection criterion.
 - c. displays more rapid progress in reducing the incidence and severity of CHD in progeny than does the DI.
 - d. is proven to be a superior hip-screening method than both dorsolateral subluxation or dorsal acetabular rim score.
 8. Information drawn from the PennHIP® database
 - a. ranks each dog relative to all other dogs in the database.
 - b. ranks each dog relative to other dogs of that particular breed.
 - c. cannot assist breeders in identifying dog owners willing to volunteer their PennHIP® information.
 - d. provides no strategies for moving the average of the population toward tighter hips with each breeding generation.
 9. High heritability (h^2)
 - a. does not affect the rate of expected genetic change in the next generation.
 - b. slows the rate of expected genetic change in the next generation.
 - c. speeds the rate of expected genetic change in the next generation.
 - d. cannot be considered applicable to the rate of expected genetic change in the next generation.
 10. Rapid genetic change for tight hips can occur when
 - a. selection pressure is applied by mating dogs with low DIs.
 - b. high DIs are used to choose breeding stock.
 - c. subjective hip scoring tests are used to select breeding dogs.
 - d. genetic control of hip laxity cannot be achieved; therefore, breeders can use any dogs in their breeding programs.