Quantitative genetics of secondary hip joint osteoarthritis in a Labrador Retriever–Greyhound pedigree

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Objective—To evaluate the quantitative inheritance of secondary hip joint osteoarthritis in a canine pedigree.

Animals—137 Labrador Retrievers, Greyhounds, and mixed-breed dogs.

Procedures—Necropsy scores ranging from 0 to 4 were obtained for each hip joint. Seven unaffected Greyhounds with normal hip joint conformation were also used for genetic modeling, but were not euthanized. Sixty-six male and 71 female dogs were allocated to 2 groups (≤ 12 months of age and > 12 months of age). Statistical models were developed to establish the inheritance pattern of hip joint osteoarthritis that developed secondary to hip dysplasia.

Results—62 dogs had evidence of osteoarthritis in a hip joint, and 75 had no evidence of osteoarthritis. After sex was adjusted for, the necropsy score was found to be inherited additively but without dominance. Each Labrador Retriever allele increased the necropsy score by 0.7 to 0.9 points, compared with the Greyhound allele, and male sex increased the necropsy score 0.74 over female sex. Approximately 10% of the variation in necropsy score was attributable to the litter of puppies' origin.

Conclusions and Clinical Relevance—Because secondary hip joint osteoarthritis is inherited additively, selection pressure could be applied to reduce its incidence. Similar statistical models can be used in linkage and association mapping to detect the genes in the underlying quantitative trait loci that contribute to hip joint osteoarthritis. (*Am J Vet Res* 2007;68:35–41)

Canine hip dysplasia is a common inherited developmental orthopedic disease of medium- and large-breed dogs that is characterized by various degrees of laxity and incongruity in the hip joint. Canine hip dysplasia is a polygenic or complex trait, the underlying molecular genetic basis of which is unknown. On the basis of population genetic analyses, it is suspected that a few major QTLs, with minor contributions from others, likely contribute to the CHD phenotype.[1] Twelve putative QTLs have been discovered that may contribute to the dysplastic phenotype within a Labrador Retriever–Greyhound crossbreed pedigree.[2] On the basis of genome-wide significance thresholds, QTLs on each end of canine chromosome CFA01 were identified that contributed separately to the left and right Norberg angle in a kindred of Portuguese Water Dogs.[3] One challenge at present is to discover the genes and their mutations that exist within these QTLs and contribute to CHD.

Hip joint osteoarthritis has generally been considered to be an inevitable sequela to CHD and, in the absence of severe traumatic injury to the hip joint, has been considered to be diagnostic for antecedent CHD. In a dysplastic hip, poor hip joint congruity and subluxation lead to abnormal focal loading and stress on articulating surfaces.[4] This leads to perifoveal articular cartilage erosion, capsular and round ligament thickening, and synovial effusion and synovitis. These early changes are undetectable radiographically but can be clinically important and lead to signs of joint pain and physical disability. Dysplastic dogs often develop lameness and gait abnormalities from 3 to 8 months of age. Subchondral sclerosis and osteophyte formation develop later in the progression of disease.[5,6] Development of these more advanced lesions is necessary for radiographic diagnosis of osteoarthritis secondary to antecedent CHD. Unfortunately, the radiographic alterations consistent with hip joint osteoarthritis develop late in disease progression and are therefore less than ideal for use in guiding selective breeding programs. Also, a dog's phenotype does not always reflect the underlying genotype; a nondysplastic dog may carry 1 or more alleles that promote CHD or secondary osteoarthritis and could therefore produce dysplastic offspring. Nongenetic or environmental influences may contribute some variation in the expression of secondary osteoarthritis, which can be exacerbated by obesity and rapid growth.[5–9]

Abbreviations

QTL	Quantitative trait locus
CHD	Canine hip dysplasia
EHR	Extended-hip radiograph

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Some breeds of dogs may tolerate passive hip joint laxity better than other breeds.[10,11] Dogs of certain breeds develop radiographically apparent hip joint osteoarthritis in association with CHD more quickly than dogs of other breeds.[10] Molecular genetic evidence for this breed effect on development of secondary hip joint osteoarthritis is beginning to emerge. A QTL for acetabular osteophyte formation secondary to CHD in Portuguese Water Dogs was detected on the CFA03 chromosome.[12] Abnormal mechanical loading associated with the severity of hip joint subluxation during ambulation is likely responsible for some of the variation observed in severity of secondary hip joint osteoarthritis. However, this finding in Portuguese Water Dogs suggests that there may be QTLs that regulate the severity of secondary hip joint osteoarthritis that are separate from or interact with those that regulate expression of CHD. Identifying the molecular genetic basis of both CHD and secondary osteoarthritis will provide a foundation for understanding the link between the 2 conditions.

Several authors have discussed the relationship between hip dysplasia and early-onset hip joint osteoarthritis in humans.[13–17] The 2000 NIH conference report on osteoarthritis stated that in humans, osteoarthritis appears to be strongly genetically determined; genetic factors account for at least 50% of the variance in cases of osteoarthritis of the hands and hip joint.[18,19] Susceptibility loci for human hip joint osteoarthritis have been mapped to several chromosomes with various levels of statistical support.[20,21] Recent evidence suggests that polymorphisms in signal transduction genes or transcriptional regulatory sequences are a major route through which osteoarthritis susceptibility is expressed locally in the joint.[21]

Quantitative (ie, complex) traits such as CHD and hip joint osteoarthritis are regulated by alleles at loci that act additively, and some alleles may also have dominance. In a Labrador Retriever–Greyhound pedigree, the inheritance pattern of the distraction index was determined to be additive, and the inheritance pattern of the dorsolateral subluxation score was both additive and dominant.[22] Knowledge of the inheritance pattern will enable the optimum statistical approach to be used for mapping the QTL regulating hip joint osteoarthritis in dogs and for identifying the genes within the QTL. The aim of the study reported here was to establish the inheritance pattern of hip joint osteoarthritis in Labrador Retrievers, Greyhounds, and their crossbred offspring in an experimental pedigree.

Materials and Methods

Pedigree—A pedigree was constructed for linkage analysis of CHD and hip joint osteoarthritis by mating dysplastic Labrador Retrievers with unaffected Greyhounds.[22–24] The 8 founder Labrador Retrievers (5 males and 3 females) were from a colony maintained at the Baker Institute for Animal Health. All but one of the Labrador Retrievers were dysplastic on the basis of EHR findings at 2 years of age. One Labrador Retriever had fair hip conformation. The 7 founder Greyhounds (2 males and 5 females) were acquired from racing stock; all had good to excellent hip conformation on EHRs obtained at 2 to 3 years of age. Greyhounds were used in the study because the breed is one of the few breeds in which hip joint conformation is consistently excellent.[25] The hips of 7 offspring of 2 of those Greyhounds were categorized as unaffected and included in the genetic analysis despite the fact that their hips were not evaluated grossly (those dogs were not euthanized). Dogs from the first filial generation (F_1) were bred back to Greyhounds and Labrador Retriever parents of other F_1 litters or were intercrossed.[22,24] In addition to the crossbreed pedigree, Labrador Retrievers that were related to the cross pedigree founders were also included in genetic analyses. The environment was standardized, and the dogs were fed to maximize growth. The study was approved by the Cornell Institutional Animal Care and Use Committee.

Assignment of necropsy score—All crossbred dogs not retained for breeding and not adopted were euthanized at 8 months of age or older with an overdose of pentobarbital sodium administered IV. Large-breed dogs are skeletally mature at 8 months of age; although 8 months of age may be too early for development of radiographic evidence of osteoarthritis, it is a reasonable age for detection of early soft tissue changes and cartilage lesions. In a previous study,[26] it was found that all dogs with dorsolateral subluxation scores < 42% (ie, with increased hip joint subluxation) had perifoveal cartilage lesions by 8 months of age. Sex and age at necropsy were recorded, and dogs were allocated to 1 of 2 age groups (≤ 12 months and > 12 months). Categories used for calculating necropsy scores have been described.[26] Osteoarthritic hip joints have increased synovial fluid volume, increased volume of the round ligament of the femoral head, and perifoveal articular cartilage fibrillation.

The hips were removed en bloc, stored on ice, and evaluated within 2 hours of euthanasia. The synovial fluid in each hip joint was aspirated. After joints were opened, any additional synovial fluid was obtained from the hip joint and the volume of synovial fluid recorded. Less than 0.3 mL of synovial fluid can be aspirated from healthy hip joints.[27] If the synovial fluid volume was ≥ 0.3 mL, the joint was assigned a score of 1; if ≤ 0.3 mL was aspirated, the joint was assigned a score of 0. The round ligament of the femoral head was excised in toto, and its volume was measured by means of water displacement. The displacement volume of a healthy round ligament in Labrador Retrievers is approximately 0.7 mL.[4] Joints with a round ligament volume > 0.7 mL were assigned a score of 1; a score of 0 was assigned if the volume was ≤ 0.7 mL. The perifoveal articular cartilage was assessed for gross evidence of fibrillation or ulceration. If the area of fibrillation was ≤ 0.5 × 0.5 cm, the cartilage was assigned a score of 1; if the area of fibrillation was ≥ 0.5 × 0.5 cm, the assigned score was 2; and if there was no lesion, the cartilage score was 0. Because articular cartilage fibrillation is a pathognomonic finding for osteoarthritis and because synovial fluid and round ligament volume measurements are more difficult to measure accurately, the finding of cartilage injury was given a higher weight, compared with the other variables. Joints were assigned a total score by addition of individual category scores. The maximum possible score for a joint was 4.

Genetic modeling—A statistical model was developed to establish the contribution of each founder breed (Labrador Retriever and Greyhound) and crossbred groups (F_1, F_2, and F_1 backcrosses to Labrador Retrievers [BCL dogs], F_1 backcrosses to Greyhounds [BCG dogs], and intercrosses between 2 BCL dogs) to development of hip joint osteoarthritis. This model attributes to each breed the proportion of genes (as a continuous variable) derived from Labrador Retrievers, Greyhounds, or F_1 dogs according to previously described methods.[22] The coefficient of the additive effect is the difference between the expected proportion of GG (Greyhound) and LL (Labrador Retriever) loci, whereas the coefficient of the dominance effect is the expected proportion of GL loci. For ease of calculation, the F_1 genotype was assigned the value of 0, the GG genotype was 1, and the LL genotype was –1. The genetic model thus incorporated a built-in contrast between the GG and LL genotypes that allowed their relative contribution to an additive and dominance mode of transmission to be tested simultaneously.[22]

The genotype effect was analyzed by further dividing the model into a left-right 2-trait model that incorporated observations of the left and right hips simultaneously as dependent variables and a single-trait model that combined observations from the left and right sides into a single variable. In the single-trait model, there were 3 possible dependent variables: the mean and the maximum and minimum observations on either the left or right side. Both of the statistical models can be described in the same format according to this equation:

$$y = X\beta + Zu + Wv + e$$

where y is the vector of observations (necropsy score); β is an unknown vector containing the fixed effects of sex, side, age at necropsy, additive effect, and dominance; u is an unknown vector of random additive genetic effect of the dog litter; X, Z, and W are the known design matrices; and e is the unobserved vector of random error. U, v, and e vectors are assumed to be normally distributed with mean and variance as follows:

$$E\begin{pmatrix}\mathbf{u}\\ \mathbf{v}\\ \mathbf{e}\end{pmatrix}=\begin{pmatrix}0\\ 0\\ 0\end{pmatrix} \quad Var\begin{pmatrix}\mathbf{u}\\ \mathbf{v}\\ \mathbf{e}\end{pmatrix}=\begin{pmatrix}\mathbf{G} & 0 & 0\\ 0 & \mathbf{T} & 0\\ \mathbf{0} & \mathbf{0} & \mathbf{R}\end{pmatrix}$$

where $G = \begin{bmatrix}\acute{o}_a^2 & \acute{o}_{12}\\ \acute{o}_{12} & \acute{o}_a^2\end{bmatrix} \otimes A$ in the 2-trait model or $G = \acute{o}_a^2 A$ in the single-trait model,

$$T=\begin{pmatrix}\mathbf{D}_1 & \cdots & 0\\ \vdots & \ddots & \vdots\\ 0 & \cdots & \mathbf{D}_m\end{pmatrix}\acute{o}_a^2, \text{ and } \mathbf{R}=\begin{pmatrix}1 & \cdots & 0\\ \vdots & \ddots & \vdots\\ 0 & \cdots & 1\end{pmatrix}\acute{o}_e^2 .$$

Operator ⊗ is the direct product of matrices, also called the Kroneker or Zehfuss product; $\acute{o}_a^2$ is the additive genetic variance; $\acute{o}_{12}$ is the additive genetic covariance; A is the relationship calculated from the pedigree by use of the tabular method; and $\mathbf{D}_i$ is a square matrix with elements of ones as follows:

$$\mathbf{D}_i=\begin{pmatrix}1 & \cdots & 1\\ \vdots & \ddots & \vdots\\ 1 & \cdots & 1\end{pmatrix} \quad \text{and i = 1 to m,}$$

where m is the number of the litter. The dimension of $\mathbf{D}_i$ is n_i by n_i, and n_i is the number of observations in the i^{th} litter. Values of $P < 0.05$ were considered significant. The measurements of necropsy score were analyzed with a mixed linear model.[a] The additive genetic variance and residual variance components were estimated with the ridge-stabilized Newton-Raphson algorithm for restricted maximum likelihood estimation.[28]

Results

Dogs and osteoarthritis—The hip joints of 130 dogs were grossly assessed at necropsy and were included in analyses (trait information was unavailable for 2 right hips); 7 dogs' hips were not assessed at necropsy but were included in the analysis, for reasons described previously. Sixty-six dogs were male, and 71 dogs were female. Ninety-two dogs were ≤ 12 months of age, and 45 dogs were > 12 months of age. Mean ± SD age at necropsy for unaffected dogs was 13 ± 9.7 months, with a range of 8 to 84 months; age at necropsy for affected dogs was 19 ± 12.8 months, with a range of 8 to 60 months. The distribution of dogs by breed and number affected in each breed was summarized (**Figure 1**). Sixty-two dogs had evidence of hip joint osteoarthritis, and 75 had no evidence of osteoarthritis. Sixteen of 22 Labrador Retrievers, 11 of 28 F_1 dogs, 7 of 14 F_2 dogs, 9 of 25 BCG dogs, 17 of 37 BCL dogs, and 2 of 2 BCL × BCL dogs had osteoarthritis in at least 1 hip joint; none of the 9 Greyhounds had evidence of hip joint osteoarthritis. The distribution of dogs by presence or absence of hip joint osteoarthritis, sex, and hip side was summarized (**Table 1**).

Because of the young age of the dogs, there were few hips with severe osteoarthritis (Figure 1). Of the 62 dogs with hip joint osteoarthritis, 21 dogs (approx 15%) were unilaterally affected. Twelve dogs were affected only in the left hip joint, 9 dogs were affected only in the right joint, and 41 dogs were bilaterally affected. Fifteen of the 21 unilaterally affected dogs were ≤ 12 months of age.

Table 1—Numbers of dogs of each sex and affected hip joint (left and right) according to necropsy score among 137 dogs (172 hip joints) evaluated for CHD and hip joint osteoarthritis. Necropsy scores were assigned on the basis of gross findings at necropsy and ranged from 0 to 4. For summary purposes, necropsy scores are given as 0 (unaffected) or > 0 (affected with hip joint osteoarthritis).

Variable	Necropsy score = 0		Necropsy score > 0	
Sex	Male	Female	Male	Female
Left	30	54	36	17
Right	32	53	32	18

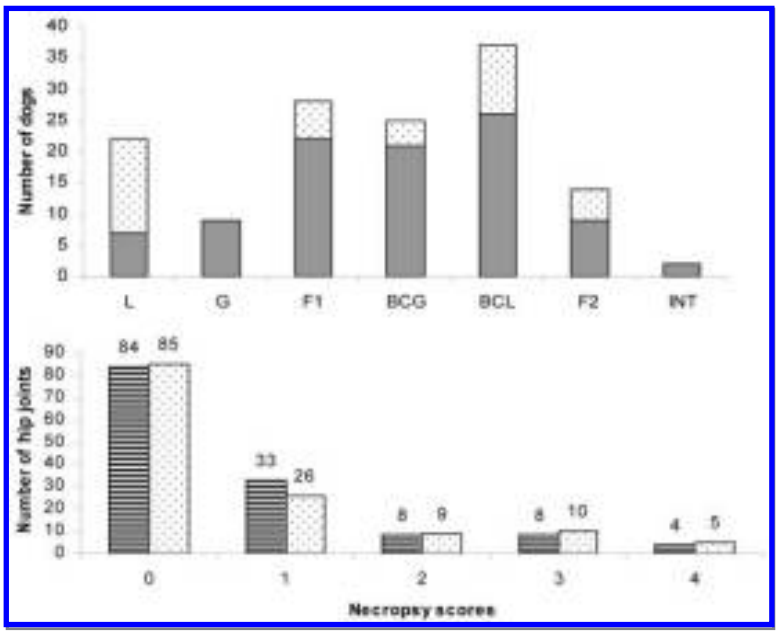

Figure 1—Histograms depicting the number of dogs affected and unaffected with osteoarthritis by breed (top panel) and the number of right and left hip joints affected by necropsy score (bottom panel) among 137 Greyhounds, Labrador Retrievers, and crossbreds. In the top panel, affected dogs are depicted by the dotted bars and unaffected dogs are depicted by the solid bars. In the bottom panel affected left hip joints are depicted by the striped bars and affected right hip joints are depicted by the dotted bars. L=Labrador Retriever. G = Greyhound. F1 = First filial generation. BCG = Backcross to the Greyhound (F1 X G). BCL = Backcross to the Labrador Retriever (F1 X L). F2 = F1 X F1. INT = Intercross (BCL X BCL).

Table 2—Estimate ± SE values of variance components for necropsy scores in the same 137 dogs as in Table 1.

Variable	Left-right	Mean	Max	Min
Genetic variance	0.29 ± 0.26	0.04 ± 0.19	–0.02 ± 0.2	0.04 ± 0.17
Covariance	–0.04 ± 0.14	NA	NA	NA
Residual variance	0.64 ± 0.17	0.68 ± 0.14	1.04 ± 0.2	0.58 ± 0.12
Litter variance	0.10 ± 0.07	0.10 ± 0.10	0.08 ± 0.1	0.12 ± 0.10
Heritability	0.28	0.04	0	0.05

Left-right = Left-right 2-trait model. Mean = Mean value for both hips. Max = Maximum hip joint score per dog. Min = Minimum hip joint score per dog.

Table 3—Summary of statistical tests used to evaluate the effects of sex, age at necropsy, and additive and dominance genetic contributions in the same dogs as in Tables 1 and 2.

	Left-right*				Mean				Max		Min	
Source	DFN	DFD	F	*P*	DFN	DFD	F	*P*	F	*P*	F	*P*
Sex	2	262	10.8	< 0.001	2†	130	11.7	< 0.001	13.2	< 0.001	9.12	< 0.001
Age at necropsy	2	262	1.35	0.261	1	130	1.29	0.258	0.9	0.344	1.38	0.243
Additive effect	2	262	9.53	< 0.001	1	130	19.3	< 0.001	24.5	< 0.001	16.1	< 0.001
Dominance	2	262	0.29	0.746	1	130	0.12	0.725	0.17	0.682	0.02	0.900

*Null hypothesis was that there was no effect within either side (left or right hip joint). †Null hypothesis was that male and female were the same within each side (left or right hip joint). DFN = Degrees of freedom in the numerator. DFD = Degrees of freedom in the denominator. F = F statistic. *P* = Probability.
See Table 2 for remainder of key.

Only 5 of 21 (24%) dogs had a necropsy score > 1; of those, 3 were older than 12 months. The mean necropsy score for the younger unilaterally affected dogs was 1.13, and mean necropsy score for unilaterally affected dogs older than 12 months was 2.4.

Inheritance of the necropsy score—Approximately 10% of the variation in necropsy scores was attributable to the litter of origin. The litter variance was similar across all models tested. However, the left-right 2-trait model had the most power to detect genetic variance at 0.29 ± SE = 0.26 (**Table 2**). After adjusting for fixed effects, the necropsy score was inherited with a significant additive genetic component and with no dominance in all models tested. Sex was a significant variable in all models (**Table 3**). Being male increased

Table 4—Estimate ± SE values for the fixed effects of sex, age at necropsy, and additive and dominance genetic components of the necropsy score of dogs.

	Left-right				
Source	**Left**	**Right**	**Mean**	**Max**	**Min**
Sex (male)	0.80 ± 0.26	0.68 ± 0.26	0.8 ± 0.20	0.98 ± 0.20	0.61 ± 0.19
Sex (female)	0.25 ± 0.26	0.17 ± 0.26	0.21 ± 0.20	0.29 ± 0.20	0.07 ± 0.19
Age at necropsy	0.01 ± 0.01	0.01 ± 0.01	0.01 ± 0.01	0.01 ± 0.01	0.01 ± 0.01
Additive	–0.90 ± 0.29	–0.73 ± 0.26	–0.9 ± 0.20	–1.03 ± 0.21	–0.85 ± 0.21
Dominance	–0.00 ± 0.24	–0.18 ± 0.23	–0.1 ± 0.20	–0.09 ± 0.22	–0.03 ± 0.21

Left = Left hip joint. Right = Right hip joint.
See Tables 2 and 3 for remainder of key.

the necropsy score by approximately 0.74 (0.80 for the left hip and 0.68 for the right hip), compared with being female (**Table 4**). Being female had no significant influence on the necropsy score because of the size of the SE. Each allele from a Labrador Retriever increased the necropsy score by 0.73 to 0.90 (depending on hip side) on the 4-point scale, compared with alleles from Greyhounds. Age at necropsy had no effect on necropsy score. The SD was too great to establish significance. This does not rule out that a significant relationship existed between age and necropsy score, but the sample size was too small to be conclusive.

Discussion

No foolproof method for diagnosing CHD, either radiographically or by clinical examination, has emerged. Radiography is an insensitive technique for detecting early hip joint osteoarthritis, and some dogs with no radiographic evidence of CHD on EHRs at early maturity (8 months of age) develop hip joint osteoarthritis later in life. The Orthopedic Foundation for Animals recommends that a radiographic diagnosis of CHD not be confirmed before 2 years of age. This later time frame allows the secondary hip joint osteoarthritis to progress and possibly become evident radiographically in those dogs that have mild forms of CHD. However, 2 years of age is generally past the start of breeding age. Although more sensitive radiographic methods have been elucidated,[26] no radiographic diagnostic method for CHD is without flaws. The difficulties with CHD diagnosis emphasize the desirability of understanding the genetic basis of hip joint osteoarthritis, as well as that of CHD. The genetic determinants that contribute to the conversion of a dysplastic hip joint to a hip joint with osteoarthritis are as yet unknown. The cross-breed pedigree used in the present study was developed to initiate understanding of this process at the molecular genetic level.[1]

The left-right hip 2-trait model best partitioned the variance into individual components, including the genetic contribution to the necropsy score. Inclusion of both hip joint scores as dependent variables in the same model yielded the maximum trait information, compared with the single-trait model, in which a mean necropsy score was calculated for both hip joints or the maximum or minimum necropsy score per dog was used. For some inherited traits, multiple-trait models for genetic locus mapping can have more power to detect a QTL than single-trait models.[29,30] However, Chase et al[3] suggested that keeping the left and right hip separate in genetic and mapping models can lead to increased power of QTL detection as the molecular genetic contribution to the left and right hip joints.

Age at necropsy had little effect on the necropsy score, a finding that was contrary to findings from our previous report.[26] Although necropsy scores tended to be higher with increasing age, the relationship was not significant. The contradiction may result in part from the fact that the models used in the present study were different than previous models. The present study was designed to determine the genetic basis of the necropsy score, whereas in the earlier study, we attempted to ascertain the relationship between the finding of osteoarthritis at necropsy and the radiographic measurements that defined the extent of CHD. Additionally, the SD of the necropsy score for the left and right hip joints was large enough in each age category that the potential contribution of age at necropsy to the necropsy score was obscured. The sample size may also have been too small to permit assessment of significance.

In the present study, we weighted the articular cartilage lesion by ascribing a score of 0 for no lesion, a score of 1 for a 0.5 × 0.5-cm lesion, and a score of 2 for larger lesions. In our experience, the presence of an articular cartilage lesion is the most sensitive indicator of an arthritic joint at gross necropsy. Measurements of synovial fluid volume and volume of the round ligament of the femoral head, although quantitative and useful, are prone to operator error in collection. A caveat to assigning presence or absence of osteoarthritis on the basis of necropsy findings in young dogs is that some of the dogs would have developed grossly visible osteoarthritis if they had lived longer. Therefore, some false-negative results for osteoarthritis were inevitable in our study. The use of histologic evaluation may have decreased the false-negative rate for osteoarthritis diagnosis.[27] As the age at which dogs underwent necropsy was not significant in any models, it is unclear how these false-negative results may have skewed our conclusions.

The litter to which a puppy belonged clearly contributed to the variance in the necropsy score. The perinatal maternal environment is known to influence musculoskeletal development, and hormones and other peptides in milk are transferred to suckling puppies.[31] This neonatal maternal effect can be long-lived.

Male dogs were more susceptible than females to hip joint osteoarthritis in the present study. It is possible that sex hormones interact with loci that contribute to the pathogenesis of osteoarthritis or that hormones affect transcriptional regulation and therefore local tis-

sue expression. Male hormones may be conducive to expression of certain loci, or female sex hormones may protect against expression. For example, when odds ratios were adjusted for various risk factors, women with long allele genotypes for estrogen receptor β and for androgen receptor genes had a significantly increased risk for osteoarthritis of the knee, compared with those carrying 1 short and 1 long or 2 short alleles.[32] The data suggest that sex should be considered in models that attempt to explain the molecular pathogenesis of hip joint osteoarthritis, especially in light of the finding that susceptibility loci influence development of hip joint osteoarthritis in women.[21,33,34] The sex effect was not a function of body weight (data not shown); we included body weight in these models and revealed that it did not significantly influence the necropsy score. However, we did not have body weights on all dogs, which reduced the power of the models. Therefore, it is not possible to conclude definitively that weight plays no role in the development of secondary hip joint osteoarthritis.

One might expect secondary hip joint osteoarthritis to be a simple consequence of CHD and the severity of the osteoarthritis to be directly related to the degree of laxity and subluxation of the hip joint. The quantitative genetics of CHD and secondary osteoarthritis affects this relationship, so that there is no direct correspondence between CHD phenotype and hip joint osteoarthritis in an individual dog, especially in dogs with intermediate phenotypes. Although the dorsolateral score and distraction index measure the degree of subluxation and laxity of the hip joint, respectively,[26] functional subluxation that occurs in a dog's hip joint during ambulation is difficult to assess. When a hip joint is found to be arthritic in an older dog, we ascribe this finding to antecedent functional hip subluxation. Findings of the present study reveal that osteoarthritis is inherited; therefore, the genetic basis of secondary hip joint osteoarthritis can be discovered. By mapping both CHD traits and hip joint osteoarthritis on the basis of molecular genetic linkage and association studies, we can address the question of why hip joint osteoarthritis progresses more quickly in some breeds with CHD than in other breeds.

We previously reported[24] that the crossbreed pedigree described in the present study had adequate power for mapping the loci that contribute to the secondary osteoarthritis of CHD. Whether the QTLs and genes within them that contribute to CHD are the same as those that regulate expression of secondary hip joint osteoarthritis remains to be seen, but they are unlikely to be identical. Putative QTLs contributing to hip joint osteoarthritis on the basis of microsatellite-based genome-wide screens have been reported.[b] The 5 chromosomes that contained QTLs contributing to hip joint osteoarthritis were on chromosomes CFA05, 18, 19, 23, and 30. It is premature to conclude that the loci contributing to CHD and those contributing to secondary hip joint osteoarthritis are all different. However, this preliminary analysis of a crossbreed pedigree suggests that there are differences in the loci contributing to the CHD trait and secondary hip joint osteoarthritis, because only CFA30 harbors a putative QTL for both CHD and osteoarthritis on the basis of chromosome-wide significance levels.[2] Our preliminary findings support earlier work[3] in which investigators reported a QTL for CHD (measured as the Norberg angle) on each end of canine chromosome 1 and also reported[12] a separate QTL for acetabular osteophyte formation on CFA03 in the same population of Portuguese Water Dogs.

Understanding the mode of inheritance of secondary hip joint osteoarthritis will enable development of optimum statistical models for coarse and fine mapping of the disease genes. Results may eventually lead to discovery of mutations or polymorphisms that contribute to or protect against development of secondary hip joint osteoarthritis. For example, polymorphisms in regulatory regions of genes contributing to osteoarthritis susceptibility, such as secreted frizzled-related protein 3, asporin, and calmodulin l, have been associated with osteoarthritis susceptibility in humans.[21] These genes would be candidate genes to assess in hip joint osteoarthritis in dogs if they fall within the mapped QTL regions. Identification of susceptibility or protective loci for secondary hip joint osteoarthritis may also enable selection of breeding dogs before the hip phenotype can be accurately measured either clinically or radiographically. This in turn could lead to improvement in hip joint conformation and subsequent reduction in CHD and secondary hip joint osteoarthritis, improving breeding programs and the quality of life for dogs and their owners.

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