Inheritance of cricopharyngeal dysfunction in Golden Retrievers

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Objective—To characterize a genetic component to cricopharyngeal dysfunction (CD) in Golden Retrievers.

Animals—117 dogs.

Procedure—The CD phenotype was determined by videofluoroscopy, and dogs were classified as affected if the upper esophageal sphincter (UES) did not open, if there were morphologic abnormalities of the UES, or if opening of the UES was delayed for ≥ 6 videofluoroscopic frames (0.2 seconds) after closure of the epiglottis. All survey radiographic and videofluoroscopic studies were reviewed by the same radiologist.

Results—Of the 117 dogs (47 males and 70 females) with a CD phenotype determined via videofluoroscopy, 21 dogs (18.0%) had abnormalities of the UES (affected). Of these 21 dogs, 9 were males (19.1% of all males) and 12 were females (17.1% of all females). The heritability of CD in a threshold model was estimated as 0.61, which established that CD could be passed from parent to offspring. Results of complex segregation analysis suggested that a single recessive allele of large effect contributed to the expression of this disease in Golden Retrievers.

Conclusions and Clinical Relevance—The determination that CD is inherited in Golden Retrievers is an important step in providing information for veterinarians attending dogs with this disorder. Breeders also require this information to make informed breeding decisions. (*Am J Vet Res* 2004;65:344–349)

The incidence of dysphagia, distinct from megaesophagus, in Golden Retrievers may have increased during the past 10 years, and clinical signs of dysphagia have recently been recognized in a colony of Golden Retrievers. Dysphagia can develop as a consequence of several cricopharyngeal disorders, including cricopharyngeal achalasia, absence of a cricopharyngeal opening, and cricopharyngeal asynchrony or dyssynchrony, which is characterized by delayed opening of the **upper esophageal sphincter (UES)** in relation to the onset of pharyngeal contraction and caudal bolus propulsion.[1-3] Positive contrast - enhanced videofluoroscopic evaluation of swallowing is useful in diagnosing **cricopharyngeal dysfunction (CD)** and differentiating it from other causes of dysphagia.[2,3]

The purpose of the study reported here was to confirm and characterize a genetic component to CD in Golden Retrievers. Videofluoroscopy was performed to determine morphologic and functional disorders of the UES. This permitted a recorded phenotype (ie, affected versus unaffected) for subsequent genetic analysis and the identification of subclinically affected dogs for exclusion from the breeding colony. Specifically, we expected to quantify the inheritance of this disorder through the estimation of heritability in a threshold model. In addition, we searched for evidence of a segregating locus with a large effect on the expression of CD through complex segregation analysis.

Materials and Methods

The Golden Retrievers evaluated in this study were patients at the Veterinary Medical Teaching Hospital, University of California, Davis. Informed client consent was obtained for all dogs. Videofluoroscopic evaluation of the swallowing reflex was performed in 117 Golden Retrievers by use of liquid barium sulfate and kibble soaked with barium sulfate. The technique used for quantitative videofluoroscopic evaluation of pharyngeal function has been previously reported as an effective method of evaluating cricopharyngeal function in the dog.[2,3] A complete physical examination was performed on each dog. Survey radiographs of the thorax including right lateral and dorsoventral projections were obtained immediately before videofluoroscopic evaluation in all dogs. Food was withheld for at least 12 hours before study initiation.

Golden Retrievers chosen for evaluation originated from a private assistance dog school, **Guide Dogs for the Blind Inc (GDB)**, and the caseload at the **Veterinary Medical Teaching Hospital (VMTH)**, School of Veterinary Medicine, University of California, Davis. All Golden Retrievers in the breeding colony at GDB were included in the study regardless of the presence or absence of clinical signs compatible with dysphagia. Subsequently, available relatives of breeding colony dogs identified via videofluoroscopy as affected with CD were chosen for inclusion in the study, regardless of the presence or absence of clinical signs suggestive of dysphagia. Any dog in the nonbreeding population of Golden Retrievers at GDB observed to have clinical signs of dysphagia was also evaluated and included in the study. Privately owned dogs from the VMTH with clinical signs of dysphagia, or without clinical signs but having 1 or more relatives with clinical signs, were included in the study. Four generation pedigrees were obtained on all dogs.

The presence or absence of clinical signs associated with CD was recorded for each dog. The CD phenotype was determined by videofluoroscopy, and dogs were classified as affected if the UES did not open, if there were morphologic abnormalities of the UES (eg, regions of persistent contraction henceforth referred to as bars), or if opening of the UES was delayed for ≥ 6 videofluoroscopic frames (0.2 seconds) after closure of the epiglottis. Results of a previous study[3]

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indicate that the mean ± SD time to opening of the UES in normal dogs was 0.09 ± 0.02 seconds after closure of the epiglottis, whereas dogs affected by cricopharyngeal asynchrony had a mean ± SD UES opening time of 0.31 ± 0.14 seconds. In this study, dogs with UES opening times > 0.2 seconds were classified as abnormal because the timing was > 2 SD from the mean of the normal population and because bulging of the piriform recess was visible prior to opening of the UES in those dogs. All radiographs and videofluoroscopic studies were reviewed by the same radiologist (REP), who was unaware of the clinical status of each dog.

The estimation of heritability, as well as the subsequent complex segregation analysis, was centered on the set of 117 Golden Retrievers with a CD phenotype (ie, affected vs unaffected) as determined by videofluoroscopy. Certain dogs were affected subclinically, meaning that they had no clinical signs of dysphagia but abnormalities of the UES were identified via videofluoroscopy. Those dogs were classified as affected because the criteria were determined on the basis of results of videofluoroscopy. By use of pedigree records from GDB, as well as pedigree information from owners of dogs evaluated at the VMTH, it was determined that the 117 dogs were related to an additional 4,810 dogs, for a total of 4,927 dogs in the data set. Although not all 4,927 dogs were evaluated for CD videofluoroscopically, they provided relationships between affected and unaffected dogs that aided in the estimation of the heritability of this disorder.

How the 117 dogs entered our study was important to the evaluation of CD inheritance. Veterinary staff of GDB evaluated all Golden Retrievers that had the potential to be future breeding dogs, whether or not the dogs had suspect pedigrees for CD. For privately owned dogs evaluated at the VMTH, however, when an affected dog was identified, relatives of the affected dog were evaluated if available. Affected dogs initially identified were called probands, and the probability that an affected dog was identified as a proband was called the ascertainment probability. This sampling process can lead to misinterpretation of inheritance and has been a concern of geneticists.[4] Throughout this study, we were aware of the influence that sampling may have had on our conclusions of inheritance.

The sampling strategy used in this study made consideration of and correction for ascertainment bias essential. In the estimation of heritability, it is important to notice that mixed linear models are capable of accommodating nonrandomly sampled data.[5] Accordingly, the estimation of the heritability of CD should not be biased by family selection, provided the dogs at the base of the pedigree (those dogs with no parents identified) can be considered as a random sample of Golden Retrievers. Because the additional 4,810 dogs included had dates of birth that extended back to 1965, we expected that selection on CD was unlikely. This is more assumption than assertion because it was not possible to create or discount a process of selection against CD or for sampling such dogs disproportionately among those dogs in the base of the pedigree, all of which had no known CD phenotype. Accordingly, our estimation of heritability proceeded as if a random sample of diagnosed dogs had been collected because it was highly unlikely that dogs in the base population had been selected on an unknown, unobserved CD phenotype.[5]

Estimation of heritability was performed by use of threshold models,[6] which are typically used for binary traits. The observation of CD was considered as y_{ij} ($y_{ij} = 0$ when unaffected; 1 when affected) for the j-th dog (j = 1, 2,…, 117) of the i-th sex (i = 1 for males; 2 for females). The assumption of threshold models was such that this categorical phenotype was assumed to be related to an underlying, unobservable continuous variate (θ) through a set of 3 fixed thresholds ($\tau_0 = -\infty$; $\tau_1 = 0$; and $\tau_2 = \infty$). The τ_1 was set to zero for computational convenience, with no loss in generality or impact on subsequent data analysis.

The model for θ is similar to any that may be used for continuous phenotypes. The algebraic form of the model is as follows:

$$\theta_{ij} = \mu + sex_i + a_j + e_{ij}$$

where θ_{ij} is an unobservable continuous variate for the j-th (j = 1, 2,…, 117) dog of the i-th sex (i = 1,2). The μ is an unknown constant, sex_i is the contribution of the i-th sex to the expression of CD, a_j is the additive genetic contribution of the j-th dog, and e_{ij} is an unknown residual. Both a_j and e_{ij} are assumed to be random effects with zero means and variances σ_a^2 (the additive genetic variance) and σ_e^2 (the residual variance), respectively. The random animal effect accounts for the covariance in phenotype of relatives and is assumed to be normally distributed multivariately, with a covariance structure based on the additive relationships among all 4,927 dogs in the data set. Because the underlying scale is unobservable, we assume that the total variance is as follows:

$$\sigma_P^2 = \sigma_a^2 + \sigma_e^2$$

where $\sigma_e^2 = 1.0$, with no loss of generality.[7-9] The heritability (h^2; that fraction of the phenotypic variation that can be attributed to genetic variation) of CD on the unobservable continuous scale can be estimated:

$$h^2 = \sigma_a^2 / (\sigma_a^2 + \sigma_e^2)$$

Estimates of σ_a^2 and σ_e^2 were determined by use of a mixed-model Bayesian strategy outlined by Sorensen et al.[9] An advantage of Bayesian methods is the ability to determine not only a point estimate of the unknown parameters (eg, heritability), but also a distributional estimate. Estimation of the distribution of the unknown parameters uses a technique of numeric integration referred to as Gibbs sampling.[10] The algorithm is determined on the basis of the iterative generation of a sequence of random variables from the known conditional distributions of the parameters, time given the likelihood function of the data. Subsequent estimates of the parameters are found in the analysis of this sequence of random variables, called the Gibbs sample. For the study reported here, a total of 250,000 samples of possible heritability was generated.[a] The estimate of heritability was obtained from the mean of every 25th iterate, after discarding the first 20,000 samples, for a total of 9,200 sample observations (ie, 9,200 = [250,000–20,000]/25).

Regressive logistic models developed for complex segregation analysis[11] were used to evaluate the possible segregation of a single locus with a large effect on the CD phenotype. Complex segregation analysis has been previously described.[12] The technique integrates Mendelian transmission genetics, allele frequency, and penetrance with the patterns of covariance among relatives expected in polygenic models of inheritance. Elston et al[13] outline criteria that must be satisfied before acceptance of the major gene model. These criteria are intended to reduce the incidence of false-positives. Fitting the variety of models required for complex segregation analysis of CD was performed by use of computer software.[b]

A family structure without loops (ie, a pedigree free of inbreeding) was required before complex segregation analysis was performed. This limitation is computational, not genetic or statistical. Therefore, the 1 large family of Golden Retrievers in the data (all 4,297 dogs had ties to each other through the 117 recorded dogs) was subdivided into smaller subfamilies to remove the loops imposed by inbreeding,

thus eliminating potentially important genetic information. The abridged pedigree of the dogs with recorded phenotypes is depicted (**Fig 1**). For simplicity, however, not all 117 dogs were included in the abridged pedigree, although all 21 affected dogs were included. Development of the complex segregation analysis subset of data began with the identification of parents, grandparents, and great-grandparents of the 117 recorded dogs (ie, ignoring relatives that went back > 3 generations). Searching back 3 generations was an arbitrary decision. Retreating further into the pedigree potentially would provide more genetic information, but also would introduce more ties among families because of the large number of inbred dogs in the data set. Three generations were chosen as a compromise between increasing the amount of genetic information in relationships and minimizing the requirement to accommodate inbreeding in the complex segregation analysis. Accordingly, inbreeding remained within this subset, which required the separation of what was 1 family into several families as a way of removing the ancestors responsible for the inbreeding. Duplication of the ancestor as a new dog made it possible to develop independent families.

At the end of this process there were 12 distinct families that included all 117 recorded dogs in a total of 250 dogs (the remaining 133 dogs were recorded with a missing CD phenotype). Certain dogs had been duplicated into > 1 family to give the computer software the impression that what was actually 1 dog was 2 different dogs. Duplicated dogs were those without a recorded CD phenotype. Although not ideal, this was the only way to evaluate this large, genetically informative family. The duplication of dogs made the detection of a major locus more difficult because dogs with known family ties were treated as unrelated dogs in the final complex segregation analysis, although the magnitude of this effect could not be estimated.

To accommodate for ascertainment bias, methods used to correct for sampling bias began with an evaluation of the sampling process. Use of an inappropriate correction for ascertainment bias can be as damaging to the interpretation of results as ignoring ascertainment bias.[14] For this reason, our analyses were performed with and without correction for ascertainment bias, with founders (ie, the oldest animals in a pedigree that do not have parents that are identified) as a conditioning subset,[15] which was an option of the computer software.[b]

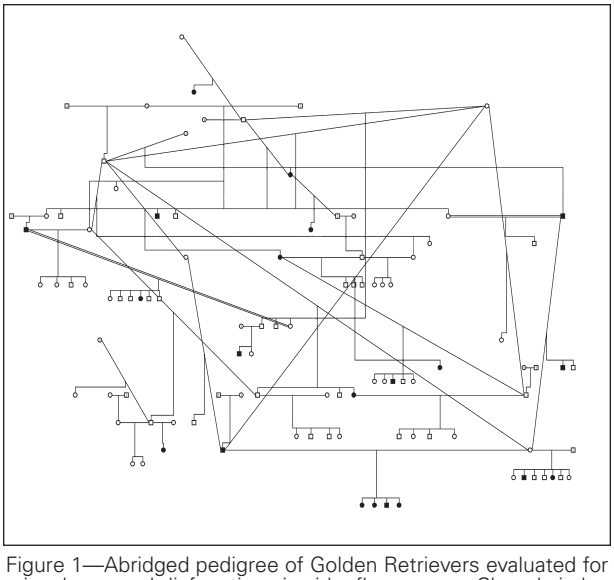

Figure 1—Abridged pedigree of Golden Retrievers evaluated for cricopharyngeal disfunction via videofluoroscopy. Closed circles = Affected female. Closed squares = Affected male.

Statistical analyses—A 2-tailed Student *t* test assuming equal variances was performed to determine significant differences in time to UES opening. For all values, $P < 0.05$ was considered significant.

Results

Of the 117 dogs (47 males and 70 females) with known phenotypes as determined by videofluoroscopy, 21 (18.0%) dogs had UES abnormalities (**Table 1**). Of these 21 dogs, 9 were males (19.1% of all males) and 12 were females (17.1% of all females), which suggested that there was no sex predilection. Among the 21 dogs with CD, 4 distinct forms of abnormal swallowing were identified. The UES never opened in 1 dog with severe clinical signs, which precluded accurate assessment of swallowing parameters. Dogs in group 1 (n = 5; no dogs with clinical signs) had a bar of tissue with persistent contraction within or immediately caudal to the UES in the proximal esophagus, although swallowing time was normal. Dogs in group 2 (n = 11; 6 dogs with no clinical signs and 1 dog with mild, 1 dog with moderate, and 3 dogs with severe clinical signs) had delayed opening of the UES in relation to the onset of swallowing. Dogs in group 3 (n = 4; 2 dogs with no clinical signs and 2 dogs with severe clinical signs) had a bar of tissue with persistent contraction in the upper esophagus and delayed opening of the UES. Dogs in group 4 were unaffected.

To further provide a general description of the data set, 1,763 of the 4,927 dogs were inbred, with a mean ± SD inbreeding coefficient of 0.031 ± 0.038. Of the 117 dogs with recorded CD phenotypes (affected or unaffected), 19 of the 21 affected dogs were inbred (mean ± SD inbreeding coefficient, 0.048 ± 0.038), and 90 of the 96 unaffected dogs were inbred (mean ± SD inbreeding coefficient, 0.025 ± 0.034). A review of the pattern of inheritance did not support the model of a simple autosomal Mendelian locus. For example, many of the affected progeny were the result of matings of 2

Table 1—Mean ± SD swallowing times for 117 Golden Retrievers with normal (unaffected) or abnormal (affected) morphology and function of the upper esophageal sphincter (UES) identified via videofluoroscopy

Groups	No. of dogs	Time to opening of UES (s)
1. Tissue bar in UES	5	0.16 ± 0.02
2. Delayed UES opening	11	0.24 ± 0.02*
3. Tissue bar in UES and delayed UES opening	4	0.23 ± 0.03*
4. Unaffected	96	0.09 ± 0.02

*Significantly ($P < 0.05$) different from unaffected dogs. The UES never opened in 1 dog with severe clinical signs of dysphagia, which precluded accurate assessment of swallowing time.

Table 2—Mean ± SD of estimates of additive genetic variance and heritability and the contrast of the effect of females with the effect of males in a threshold model for cricopharyngeal dysfunction in Golden Retrievers

	Mean	SD	95% CI
Genetic variance	1.71	0.74	0.83–3.54
Heritability	0.61	0.10	0.45–0.78
Females–males	0.12	0.44	–0.72–0.98

Estimates were obtained from a Gibbs sample of 9,200 values. CI = Confidence interval.

unaffected parents, which eliminated models of a single dominant CD allele. Discarding a model of a single recessive autosomal allele was more problematic because there were no matings of 2 affected dogs.

Mean ± SD heritability of CD from the Gibbs sample was 0.61 ± 0.10 (95% confidence interval, 0.45 to 0.78; **Table 2**). Mean ± SD difference for the effect of sex (effect of females – effect of males) on CD, on the underlying scale, was estimated as 0.12 ± 0.44 (95% confidence interval, –0.72 to 0.98). An interval spanning zero (0.0) is evidence that there were no significant differences in the expression of CD between sexes.

The complex segregation analysis with ascertainment correction in which the 5 dogs with a bar of abnormal tissue in the UES were treated as affected with the CD phenotype was performed (**Table 3**). The recessive major locus model with Mendelian transmission of the putative alleles provided a significantly ($P < 0.018$) better fit than a no major locus model. For this comparison, the log of the likelihood ratio follows:

$$-2(-65.47 - [-61.45]) = 8.04$$

with 2 degrees of freedom. A recessive major locus model in which the transmission probabilities were estimated from the pattern of inheritance displayed within the data did not provide a significantly better fit than the recessive model with fixed Mendelian transmission probabilities (ie, -2(-61.45 – [-61.09]) = 0.72, with 3 degrees of freedom; $P < 0.868$).

The complex segregation analysis with ascertainment correction in which the 5 dogs with a bar of abnormal tissue in the UES were treated as unaffected with the CD phenotype was also performed (**Table 4**). The intent of this alternative evaluation of the CD diagnosis was to evaluate how important the diagnosis may have been to any genetic interpretation. Results of this analysis indicate that there was significant ($P < 0.039$) evidence for the presence of a major locus with an impact on CD. The key comparison was between the no major locus model and that of the recessive major locus model with Mendelian transmission of the puta-

Table 3—Parameter estimates (± SE) from the logistic regression model in complex segregation analysis with ascertainment correction in which the 5 Golden Retrievers with a persistent bar of tissue in the UES were treated as affected with the cricopharyngeal dysfunction phenotype.

	Recessive major locus					
	No major locus		Mendelian transmission		Arbitrary transmission	
Parameter	Estimate	SE	Estimate	SE	Estimate	SE
p(A)	NA	NA	0.32	0.16	0.21	0.15
Pooled base	–1.50	0.35	NA	NA	NA	NA
AA base	NA	NA	7.41	5.86	9.37	6.86
AB base	NA	NA	–2.66	0.85	–5.80	5.41
BB base	NA	NA	–2.66	0.85	–5.80	5.41
τ_{AA}	NA	NA	1.00	Fixed	1.00	0.00
τ_{AB}	NA	NA	0.50	Fixed	0.57	0.15
τ_{BB}	NA	NA	0.00	Fixed	0.14	0.08
Parent regression effect	0.14	0.26	–0.26	0.44	–1.71	2.64
ln(L)	–65.47		–61.45		–61.09	

AA base, AB base, and BB base are the estimated genotypic means in the logistic model at the putative major locus, where the probability of transmitting the A allele for each genotype AA, AB, and BB is τ_{AA}, τ_{AB}, and τ_{BB}, respectively.
p(A) = Frequency of the putative major allele A. ln(L) = Natural log of the likelihood ratio. Fixed = Transmission probabilities remain constant, set to the values of Mendelian inheritance. NA = Not applicable.

Table 4—Parameter estimates (± SE) from the logistic regression model in complex segregation analysis with ascertainment correction in which the 5 Golden Retrievers with a persistent bar of tissue in the UES were treated as unaffected with the cricopharyngeal dysfunction phenotype.

	Recessive major locus					
	No major locus		Mendelian transmission		Arbitrary transmission	
Parameter	Estimate	SE	Estimate	SE	Estimate	SE
p (A)	NA	NA	0.25	0.09	0.03	0.01
Pooled Base	–1.47	0.35	NA	NA	NA	NA
AA Base	NA	NA	9.71	5.17	11.45	9.68
AB Base	NA	NA	–2.42	0.63	–3.93	4.88
BB Base	NA	NA	–2.42	0.63	–3.93	4.88
τ_{AA}	NA	NA	1.00	Fixed	1.00	0.00
τ_{AB}	NA	NA	0.50	Fixed	0.86	0.23
τ_{BB}	NA	NA	0.00	Fixed	0.17	0.11
Parent regression effect	0.34	0.29	–1.08	0.42	–0.43	1.96
ln(L)	–59.75		–56.51		–54.28	

See Table 3 for key.

tive alleles. For this comparison, the log of the likelihood ratio was as follows:

$$-2(-59.75 - [-56.51]) = 6.48$$

with 2 degrees of freedom. The model of estimated transmission probabilities did not provide a significantly better fit, leading to the general conclusion for evidence of a segregating major locus. Mean ± SD heritability of CD from the Gibbs sample when the 5 dogs with a bar of persistent contraction in the UES and normal swallowing times were evaluated as unaffected was 0.69 ± 0.09 (95% confidence interval, 0.47 to 0.86).

Discussion

In humans, CD causes a variety of clinical signs ranging from globus pharyngeus (the feeling of a lump in the throat) to dysphagia.[16-18] Morphologic abnormalities identified via videofluoroscopy in humans include pharyngeal masses, pharyngeal diverticuli, and UES impressions or bars.[16,18] Functionally, these patients have delayed opening[19,20] or premature closure[17] of the UES in relation to caudal bolus propulsion. Quantitative videofluoroscopic assessment of normal and abnormal swallowing times has been reported by use of various identifiable events to signify the onset of swallowing and other significant markers of bolus propulsion.[19,20] Johnson et al[20] chose the initiation of movement of the bolus to represent the onset of swallowing and the return of the epiglottis to its normal position to represent the end of swallowing. In that study, the normal mean ± SD bolus transit was 1.0 ± 0.15 seconds. Substantial delays in total swallowing times were identified in stroke patients with dysphagia with a mean ± SD bolus transit time of 6.15 ± 6.33 seconds.[20]

In dogs, CD has traditionally been divided into 3 categories: failure of the UES to open (achalasia), delayed UES opening (cricopharyngeal asynchrony), and failure of the UES to close (chalasia).[2] Cricopharyngeal asynchrony may be the most common of the UES disorders in dogs.[21] Regardless, videofluoroscopy has been the gold standard for evaluating UES structure and function.[2,3] A delay in the time to UES opening and total swallowing time has been reported in dogs affected with cricopharyngeal asynchrony.[3] Normal and abnormal swallowing times reported in the literature are shorter for dogs than those reported for humans. This is partially because of the choice of event to represent the onset of swallowing. At our institution and in the study reported here, the onset of swallowing was identified as closure of the epiglottis. This event was chosen on the basis of ease of identification; however, it occurs later in the swallowing process than the first movement of the bolus, as reported by Johnson et al.[20] Species differences may also explain variability in reported swallowing times.

In our study, we identified 4 categories of abnormal UES function. The UES never opened in 1 dog and likely represented a true case of cricopharyngeal achalasia. Another group of dogs had delayed opening of the UES in relation to caudal bolus propulsion, which was likely caused by cricopharyngeal asynchrony. However, we have identified a new subset of dogs (n = 9) with UES-associated or upper esophageal-associated bars similar to those reported in humans. Certain of these dogs had significantly delayed swallowing times (n = 4), whereas others did not (5). Seven of the 9 dogs with UES bars identified via videofluoroscopy did not have clinical signs of dysphagia. In humans, the UES bars have been associated with globus pharyngeus,[16] which is difficult to measure in dogs. Thus, the absence of clinical signs in dogs in our study may have been caused by an inability to detect the clinical abnormality.

Whether the various abnormalities identified via videofluoroscopy described in the study reported here were caused by a solitary genetic mutation is unclear. Dogs in which the UES did not open may represent the most severe form of delayed UES opening. Although not normal, dogs with a bar of tissue and no delay in UES opening made it difficult to score this trait for any genetic evaluation. Exclusion of these dogs from the logistic regression model did not change the overall outcome and conclusion that CD is inherited in Golden Retrievers. However, the presence of the UES bar in such a high number of dogs with delayed UES opening (n = 4) suggested an association between those abnormalities identified via videofluoroscopy. Cricopharyngeal dysfunction may result from a complex combination of genetic mutations that occur in various combinations. Regardless, during the past 5 years, exclusion of dogs with clinical signs of dysphagia and dogs with no clinical signs but with functional or morphologic abnormalities identified via videofluoroscopy has resulted in elimination of dysphagia from the GDB breeding colony. The implication of the biased sampling on the evaluation of inheritance must be considered at several levels. For the purpose of estimating heritability, the bias should be minimal. Estimation of genetic variances with mixed-model methods in data that has been subjected to selection is unbiased when the base population can be considered as a random sample.[5] Thus, although this set of data is actually 1 large family, we anticipated that the oldest dogs in the family had not been subjected to selection on CD. Nevertheless, we were concerned with the influence sampling had on our estimate of heritability. The limited sample size can also influence phenotypic variance and, consequently, our estimates of residual variance. Because the dogs were all from 1 animal facility, the possibility existed that the large heritability resulted more from a small residual variance than a large genetic variance. Accordingly, additional investigations of CD in other populations of Golden Retrievers are warranted.

The influence of ascertainment bias on complex segregation analysis is difficult to evaluate. Because these data were not obtained from a randomly sampled cluster of Golden Retrievers, we were left with an analysis determined on the basis of assumptions that could not be objectively evaluated, although the interpretation of inheritance may depend on the means of ascertainment correction.[14]

Although results of the study reported here indicate that CD in Golden Retrievers is inherited, the evidence for the presence of a single major gene affecting

the disorder was not overwhelming. In a review of complex segregation analysis, Jarvik[22] suggested prudence in the interpretation of complex segregation analysis until several sets of data had confirmed or rejected the presence of a Mendelian locus. Therefore, we conclude that CD is highly heritable, although the exact genetic mechanism that leads to expression of CD cannot be stated with certainty. The small sample size precluded drawing definitive conclusions. In addition, the breaking of inbreeding loops, necessary for the complex segregation analysis, may have influenced our conclusions of major locus effects. Moreover, the importance of the accuracy of the clinical diagnosis cannot be underestimated. The evaluation of the inheritance of any disease depends on the accuracy of the diagnosis.

Although results of this study indicated a genetic basis for CD in Golden Retrievers as evidenced by the significantly large heritability estimate, the data did not include the age of onset of CD. This reflects the diffuse nature of the clinical signs of CD and the delay between the onset of clinical signs and a definitive diagnosis. The lack of a distinct age of onset coupled with the potential delay between onset and diagnosis with appropriate treatment underscores the need to select dogs with unambiguous genetic backgrounds free of this disorder for breeding purposes. The occurrence of affected dogs without clinical signs suggests that screening of all potential breeders by videofluoroscopy is the best method to reduce the incidence of the disorder in a population of dogs.

The determination that CD is inherited in Golden Retrievers is an important step in providing information for veterinarians attending dogs with this disorder. Breeders and genetic counselors also require this information to make informed breeding decisions that will minimize the incidence of this disorder. Concrete evidence of a genetic basis for CD may be important to the selection of future breeding animals.

[a]Multiple Trait Gibbs Sampler for Animal Models (MTGSAM), USDA, Meat Animal Research Center (USMARC), Clay Center, Neb. Available at: www.aipl.arsusda.gov/curtvt/mtgsam.html. Accessed Oct 1, 2002.

[b]Statistical Analysis for Genetic Epidemiology, Release 3.1, Department of Epidemiology and Biostatistics, Rammelkamp Center for Education and Research, MetroHealth Campus, Case Western Reserve University, Cleveland, Ohio. Statistical Analysis for Genetic Epidemiology is supported by US Public Health Service Grant (1 P41 RR03655) from the National Center for Research Resources. Available at: www.darwin.cwru.edu/index.php. Accessed Jul 1, 2001.

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