Inheritance of hypoadrenocorticism in Bearded Collies

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Objective—To assess heritability and mode of inheritance for hypoadrenocorticism in Bearded Collies.

Animals—635 Bearded Collies.

Procedures—Dogs were classified as affected by hypoadrenocorticism or unaffected. Phenotypic and pedigree data were analyzed. Heritability was estimated by use of Bayesian statistical methods. Regressive logistic models for complex segregation analyses were used to characterize mode of inheritance.

Results—Hypoadrenocorticism was diagnosed in 60 (9.4%) dogs. Heritability of hypoadrenocorticism was estimated to be 0.76 with both sexes affected with equal probability. Evaluation of the pedigrees did not support a Mendelian autosomal dominant mode of inheritance. Evidence from the complex segregation analysis for a single locus of large effect on hypoadrenocorticism was not convincing.

Conclusions and Clinical Relevance—Hypoadrenocorticism in Bearded Collies is highly heritable. Although a precise genetic mechanism responsible for inheritance of the disorder remains undetermined, breeding decisions must include consideration of the genetic likelihood of passing on this deleterious disorder to offspring of affected dams and sires. (*Am J Vet Res* 2002;63:643–647).

Hypoadrenocorticism is a disorder characterized by failure of the adrenal cortex to produce sufficient hormones. The disease is classified into 2 forms, primary hypoadrenocorticism and secondary hypoadrenocorticism, on the basis of the cause of the hormonal deficit. In primary hypoadrenocorticism, the adrenal cortex becomes atrophied and incapable of hormonal production,[1] whereas secondary hypoadrenocorticism is attributable to an insufficiency of ACTH from the anterior pituitary gland to stimulate adrenal cortex function.[1-3] Primary hypoadrenocorticism is diagnosed by evaluating concentrations of glucocorticoids in the blood that are produced by the adrenal cortex in response to ACTH stimulation. Failure of ACTH to induce glucocorticoid production and release is diagnostic of primary hypoadrenocorticism. Because steroids synthesized by the adrenal cortex maintain key metabolic processes, inadequate amounts of glucocorticoids affect gluconeogenesis and energy balance. Thus, the clinical signs of hypoadrenocorticism include generalized lethargy, inappetence, and weight loss.[4,5]

Hypoadrenocorticism occurs in humans at a rate of about 1 case/100,000 people; there does not appear to be a bias with regard to race or age. In humans, hypoadrenocorticism is suspected to be the consequence of autoimmune destruction of the adrenal cortex, thereby destroying the capacity for the production of glucocorticoids and mineralocorticoids.[6] A genetic predisposition for autoimmune-mediated hypoadrenocorticism has been confirmed in humans.[7] Other suspected causes of hypoadrenocorticism in humans include infection, cancer,[8] and disorders of the pituitary gland.[9]

The frequency of hypoadrenocorticism in dogs greatly exceeds that seen for humans. It has been estimated that hypoadrenocorticism is 100 times more frequent in dogs than humans. Comparable to the disorder in humans, autoimmune destruction of the adrenal cortex has also been reported in dogs.[10] Gradual destruction of the adrenal cortex may account for inconsistency in the progression of hypoadrenocorticism among affected dogs and may be related to the variable age of onset that ranges from 6 months to 8 years.[3] Additionally, clinical signs of hypoadrenocorticism are diffuse, often resulting in a delay in obtaining a definitive diagnosis. A delay in diagnosis and implementation of treatment can have severe consequences for affected dogs. Furthermore, although hormonal replacement therapy is the treatment of choice, the cost of such therapy can be prohibitive. Given that hypoadrenocorticism in humans reflects a genetic predisposition to autoimmune disturbances, dog breeders would like to know whether a similar cause exists for dogs.

As mentioned previously, hypoadrenocorticism occurs in the entire dog population,[2,11] but certain breeds have a higher than is expected prevalence. For example, a preliminary study[12] initiated by Bearded Collie breeders revealed that the estimated incidence rate for that breed is 3.4%. Hypoadrenocorticism is believed to have a genetic basis in 31 breeds of dogs, although the mode of inheritance is undetermined.[13] The study reported here represents analysis for a number of hypoadrenocorticism-affected and unaffected Bearded Collies to characterize the genetic component of hypoadrenocorticism. Specifically, we wanted to quantify the inheritance of hypoadrenocorticism through the estimation of heritability in a threshold

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model. In addition, we used complex segregation analysis to search for evidence of a segregating locus with a large effect on the expression of hypoadrenocorticism.

Materials and Methods

Animals—Dogs included in the study were hypoadrenocorticism-affected and unaffected Bearded Collies. The dogs were designated as phenotypically hypoadrenocorticoid only when a diagnosis was made by a veterinarian after administration of an ACTH stimulation test. That test evaluates the integrity and competence of the adrenal glands through analysis of blood cortisol concentrations before and after ACTH stimulation. Results for an ACTH stimulation test in a clinically normal dog would be a baseline value (before stimulation) of 0.5 to 4.0 µg of cortisol/dl and a cortisol concentration after ACTH stimulation of 8.0 to 20 µg/dl. Dogs with hypoadrenocorticism are characterized by a lack of response to ACTH stimulation.[1] Owners mentioned that clinical signs of lethargy, vomiting, or collapse prompted them to have their Bearded Collies tested for hypoadrenocorticism.

The data set consisted of 1,249 dogs. Of these, 635 had known hypoadrenocorticoid phenotypes, and the remaining 614 dogs with unknown phenotypes were included to construct appropriate pedigrees. Dogs included in the analyses comprised 92 dogs < 2 years of age, 140 dogs between 3 and 4 years of age, and 403 dogs ≥ 5 years of age. Along with the hypoadrenocorticoid phenotype, information about sex, sire and dam, and other accompanying illnesses of each dog, if mentioned, were recorded. The matrix of numerator relationships was constructed[14] by using information for the 1,249 dogs and their sires and dams. Sorting this matrix into independent groups of relatives established a set of 186 families that ranged in size from 3 dogs (ie, sire, dam, and 1 progeny) to 30 dogs. Of the 186 families, 146 did not contain any dogs known to have hypoadrenocorticism. Of the 40 families with dogs that had hypoadrenocorticism, 19 had full phenotypic information for the dogs of 2 generations, 14 had full phenotypic information for 3 generations, and 7 had full phenotypic information for 4 generations of dogs in the pedigrees.

The number of unaffected families had bearing on subsequent analyses and the consideration of ascertainment bias. Many data sets in disease genetics are constructed around affected animals (ie, probands). The set of data reported here, however, is somewhere between a random sample and a proband-centered analysis. Methods of correcting for ascertainment bias assume that families without any affected animals have not been sampled. Moreover, among those families with affected members, appropriate correction for ascertainment bias requires knowledge of the manner in which families were included in the sample (ie, ascertained). Use of an inappropriate correction for ascertainment bias can be as damaging to the interpretation of results as ignoring ascertainment bias.[15] Accordingly, our analyses were conducted with and without correction for ascertainment bias.

Statistical analysis—To establish and quantify the inheritance of hypoadrenocorticism, we estimated the heritability of hypoadrenocorticism as a binary phenotype (eg, affected vs unaffected dogs). To accomplish this, we used threshold models of disease inheritance.[16] Our intent was to estimate the heritability of hypoadrenocorticism on a continuous, underlying, unobservable scale.

We considered the observation of hypoadrenocorticism to be y_{ij} (y_{ij} was 0 when unaffected and 1 when affected) for each specific dog j (values of j ranged from 1 to 635) of a particular sex i (value of i was 1 for males and 2 for females). The assumption of threshold models is such that this categorical phenotype was assumed to be related to an underlying, unobservable, continuous variate (ie, θ) through a set of 3 fixed thresholds (ie, τ_0, τ_1, and τ_3; value for τ_0 was $-\infty$, value for τ_1 was 0, and value for τ_3 was ∞). As θ increased in value as a consequence of combined genetic and environmental contributions (similar to any other continuous normally distributed trait) and crossed the threshold τ_1, the phenotype we observed changed from unaffected to affected. Notice that τ_1 was given a value of 0 for computational convenience without loss in generality or impact on subsequent data analysis.

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

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

where θ_{ij} is an unobservable continuous variate for the specific dog j (j = 1 to 635) with sex i (i = 1 or 2), μ is an unknown constant, sex_i is the contribution of sex to the expression of hypoadrenocorticism, a_j is the additive genetic contribution of that specific dog, and e_{ij} is an unknown residual. Both a_j and e_{ij} were assumed to be random effects with means of 0 and variances of σ_a^2 (ie, additive genetic variance) and σ_e^2 (ie, residual variance), respectively. The random effect of dog accounted for the covariance in phenotype of relatives and was assumed to be multivariately normally distributed with a covariance structure based on the additive relationships among all 1,249 dogs in the data set. Because the underlying scale was unobservable, we assumed that the total variance (σ_P^2) was equal to $\sigma_a^2 + \sigma_e^2$ and that σ_e^2 was equal to 1.0 without a loss of generality.[17-19] Notice that heritability (h^2) of hypoadrenocorticism on the unobservable continuous scale can be estimated as $\sigma_a^2/(\sigma_a^2 + \sigma_e^2)$.

Because of the questions of family ascertainment, it is important to mention that mixed linear models are capable of accommodating nonrandomly sampled data.[14] Accordingly, estimation of the heritability of hypoadrenocorticism should not have been biased by family selection, provided the dogs at the base of the pedigree (those dogs in which the parents were not identified) were considered a random sample of Bearded Collies. Of course, this was more assumption than assertion, because it was not feasible to create or discount a process of selection against hypoadrenocorticism or for sampling such dogs disproportionately among those dogs in the base of the pedigree, all of which had an unknown phenotype.

To arrive at estimates of σ_a^2 and σ_e^2, we used a mixed model Bayesian strategy outlined by Sorensen et al.[19] An advantage of Bayesian methods is the ability to arrive at a point estimate of the unknown parameters (eg, heritability) as well as a distributional estimate. Estimation of the distribution of unknown parameters used a technique of numeric integration referred to as Gibbs sampling.[20] The algorithm was based on the iterative generation of a sequence of random variables from the known conditional distributions of the parameters, given the likelihood function of the data. Subsequent estimates of the parameters were found in the analysis of this sequence of random numbers, called the Gibbs sample. In this analysis, we generated 250,000 samples of possible heritability. Our estimate of heritability was taken from the mean of every 25th iterate, after discarding the first 20,000 samples, for a total of 9,200 sample observations (ie, [250,000 – 20,000]/25). The Gibbs sampling process and the theoretic basis for the analysis have been described elsewhere.[19-21]

To evaluate the possible segregation of a single locus with a large effect on the hypoadrenocorticism phenotype, we used regressive logistic models developed for complex segregation analysis.[22] Complex segregation analysis has been described in detail elsewhere.[23] The technique is intended to integrate Mendelian transmission genetics, allele frequency, and penetrance with the patterns of covariance among relatives expected in polygenic models of inheritance. Elston et al[24] outlined

criteria that must be satisfied before acceptance of the major gene model; these criteria are intended to reduce the incidence of false-positive results. Fitting of several models necessary for complex segregation analysis of a binary trait was conducted by use of genetic epidemiologic software.[a]

Prior to complex segregation analysis, the genetic epidemiologic software required a family structure that had a pedigree free of inbreeding (ie, without loops). This limitation was computational, not genetic or statistical. Accordingly, several large families of Bearded Collies that harbored inbreeding had to be subdivided into smaller subfamilies to remove the inbreeding loops, thus eliminating important genetic information. Although not ideal, this was considered the only way to include these large and otherwise genetically informative families in the analysis. The impact on the final complex segregation analysis made the detection of a major locus more difficult, although the magnitude of this effect was not estimable.

Results

Of the 635 dogs (272 males, 363 females) with known hypoadrenocorticoid phenotypes, 60 (9.4%) had clinical signs of hypoadrenocorticism. Age distribution for the dogs with hypoadrenocorticism was as follows: < 2 years of age, 1 dog; between 3 and 4 years, 7; ≥ 5 years of age, 49. Birthdate was not recorded for 3 dogs. Of these 60 dogs, 24 were males (8.8% of all males), and 36 were females (9.9% of all females), suggesting that there was little difference in the prevalence of this disorder on the basis of sex.

A review of the pattern of inheritance did not support the model of a simple autosomal dominant Mendelian locus. For example, many of the affected progeny were the result of a mating between 2 unaffected dogs, eliminating models of a single dominant allele for hypoadrenocorticism. Discarding a model of a single recessive autosomal allele was more problematic, because we did not have a mating between 2 affected dogs.

Results from the analysis of the threshold model, including an estimate of the heritability of hypoadrenocorticism on the underlying unobservable scale, were reported. Mean ± SD additive genetic variance was 3.44 ± 1.05 (95% **confidence interval [CI]**, 1.96 to 6.13). Mean heritability of the Gibbs sample (9,200 values) was 0.76 ± 0.05 (95% CI, 0.66 to 0.85). Clearly, the disorder was influenced by mechanisms passed from parent to offspring and was of sufficient magnitude that selection against the disease should be successful. In fact, a heritability of this order is suggestive of the segregation of a single locus of large effect. Morton and MacLean[25] documented that major loci tend to increase the heritability of a trait in a given population, and a value of 0.76 is comparatively large for many polygenic traits.

Results also provided evidence for equality in the prevalence of hypoadrenocorticism for both sexes. Mean difference in sexes on the underlying scale was estimated as 0.12 ± 0.29, with an empirical 95% CI of –0.44 to 0.69. A 95% CI that spans 0 was clear evidence that there were not any differences in the expression of hypoadrenocorticism on the basis of sex.

Results of the complex segregation analysis were determined (**Table 1**). First, we noticed that the model for the recessive major locus (with Mendelian transmission of the putative alleles) provided a significantly (P = 0.024) better fit than the model for lack of a major locus. For this comparison, logarithm of the likelihood ratio was –2 (–226.06 – [–222.29]) = 7.54 with 2 degrees of freedom. However, a model for a recessive major locus in which the transmission probabilities were estimated from the pattern of inheritance displayed within the data provided a significantly (P = 0.004) better fit than the recessive model with fixed Mendelian transmission probabilities (ie, –2 [–22.29 – {–215.68}] = 13.22 with 3 degrees of freedom). As suggested by Elston et al,[24] this contrast between the 2 models reduces the probability of falsely declaring a major locus. Obviously, alleles at a genuine major locus would have to be transmitted from parent to offspring with probabilities that reflect Mendelian transmission. Our results document that a better fit to the data can be provided when the probabilities of transmission are significantly different from those expected for standard Mendelian transmission. Accordingly, we concluded that a major locus with an impact on hypoadrenocorticism cannot be established with the data reported here.

Table 1—Estimates and SE obtained from the logistic regression model used in complex segregation analysis of hypoadrenocorticism in a cohort of Bearded Collies

	Lack of a major locus		Recessive major locus—Mendelian transmission		Recessive major locus—arbitrary transmission	
Variable	**Estimate**	**SE**	**Estimate**	**SE**	**Estimate**	**SE**
p(A)*	NA	NA	0.21	0.03	0.25	0.03
Pooled base	–2.93	0.17	NA	NA	NA	NA
AA base	NA	NA	6.38	3.71	4.08	2.02
AB base	NA	NA	–3.59	0.85	–3.40	0.31
BB base	NA	NA	–3.59	0.85	–3.40	0.31
τ_{AA}†	NA	NA	1.00	Fixed	0.56	0.97
τ_{AB}‡	NA	NA	0.50	Fixed	0.98	0.44
τ_{BB}§	NA	NA	0.00	Fixed	0.13	0.05
Parent regression‖	0.32	0.21	0.53	0.23	–3.53	0.28

*Frequency of the putative major allele A. †Transmission probability for homozygous putative allele A. ‡Transmission probability for heterozygous alleles. §Transmission probability for homozygous allele B. ‖Regression effects attributable to parents.

NA = Not applicable.

Natural logarithm of the likelihood for lack of a major locus, recessive major locus-Mendelian transmission, and recessive major locus-arbitrary transmission was –226.06, –222.29, and –215.68, respectively

Discussion

The progression and age of onset of hypoadrenocorticism varies among dogs. Additionally, the clinical signs are diffuse, resulting in variable diagnoses until a definitive diagnosis can be established. The delay in establishing a definitive diagnosis and subsequent implementation of treatment can adversely affect the overall well-being of affected dogs. Furthermore, although hormonal treatments exist, the implementation of such treatments can be costly for owners. Thus, elimination of the disorder is preferred. To minimize or eliminate hypoadrenocorticism, its underlying cause must be elucidated. Although it has been presumed that hypoadrenocorticism is genetically determined in

many breeds of dogs,[13,26] statistical evidence has not been published.

A health survey of Bearded Collies in the United States revealed an incidence of hypoadrenocorticism of 3.4%.[12] The higher incidence of hypoadrenocorticism in the study reported here (9.4%) likely represents a biased sampling of dogs submitted by owners and breeders concerned about the amount of hypoadrenocorticism in this breed. Thus, owners or breeders of dogs with hypoadrenocorticism were more likely to participate in our study, thereby skewing the data. Therefore, an incidence of 9.4% does not represent the population at large. Fortunately, this bias did not preclude the use of the data for determining the genetic basis of hypoadrenocorticism in Bearded Collies.

Implications of this 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 have been subjected to selection is unbiased when the base population can be considered a random sample.[14] The impact of ascertainment bias on complex segregation analysis is less simply evaluated. Because these data were not a randomly sampled cluster of Bearded Collies, nor was it a proband-based set of families, we were left with an analysis on the basis of assumptions that cannot be objectively evaluated. We did not perform a complex segregation analysis with ascertainment bias correction with founders as a conditioning subset,[27] an option available in the epidemiologic software. This potential correction, however, did not have an impact on the conclusions drawn from our results. Thus, our conclusions were that the model of non-Mendelian transmission provided the best fit, thus violating criteria established for the declaration of the segregation of a major locus.[24]

Although analysis of the data set clearly revealed a genetic basis for hypoadrenocorticism in Bearded Collies as evidenced by the large heritability estimate, the data did not define the age of onset. Again, this reflected the diffuse nature of the clinical signs of hypoadrenocorticism and the delay in onset of those signs and establishment of a definitive diagnosis. In our study, the percentage of dogs with hypoadrenocorticism increased with increasing age. For example, only 1.1% of dogs < 2 years of age had hypoadrenocorticism, compared with 5 and 12.2% for dogs that were 3 to 4 years of age and ≥ 5 years of age, respectively. Thus, our analyses represent a conservative approach, because some young dogs classified as unaffected may develop hypoadrenocorticism with advancing age. Lack of a distinct age of onset coupled with the delay between onset of clinical signs and establishment of a definitive diagnosis with appropriate treatment underscores the need to select parents specifically to prevent passing on the disorder.

In humans, hypoadrenocorticism has been attributed to a genetic predisposition of the immune system to target the adrenal glands for destruction.[7] In particular, patients with hypoadrenocorticism possess characteristic autoantibodies specific for critical enzymes in the steroidogenesis pathway of the adrenal glands,[28] suggesting that the enzymes themselves serve as potent autoantigens for the immune system. It has been suggested that the inheritance of certain immunoglobulin genes may be responsible for immune-mediated self-destruction. Alternatively, the genetic predilection may lie within the adrenal glands, predisposing them to be an immune target. The presumed progression is initiated by a nonspecific, inflammatory episode that leads to the immune system's involvement and gradual impairment of the adrenal glands.[7]

Although analysis of the data reported here and in other studies has not revealed an association between other autoimmune disorders and hypoadrenocorticism in Bearded Collies, it is possible that this may reflect incomplete health information recorded by owners. Despite the fact that 3 dogs were reported as hypothyroid and hypoadrenocorticoid, the vast majority of dogs were unknown with respect to thyroid hormonal status. It is entirely possible that many organs are undergoing simultaneous attack by the immune system; each organ may have differential susceptibility, with the adrenal glands most strongly affected. Alternatively, the autoimmune target may be restricted to the adrenal glands; this would be consistent with the data reported here.

Although hypoadrenocorticism in Bearded Collies is definitely inherited, the evidence is not convincing for a single major gene affecting the disorder. This may be attributable to the conservative analyses and inclusion of younger dogs. The evidence is sufficient to warrant further investigation through linkage studies. Accordingly, although we can conclude that hypoadrenocorticism is highly heritable, the exact genetic mechanism that leads to expression of this disease cannot be stated with certainty. If hypoadrenocorticism in dogs is similar to that in humans, the inability to conclusively determine a major gene may reflect involvement of the immune system with the complex patterns of inheritance.[29] Such complexities have been implicated in the inheritance of other immune-mediated disorders such as inflammatory bowel disease.[30]

The determination that hypoadrenocorticism is inherited in Bearded Collies is a critical step in providing information for veterinarians attending dogs with this disorder. Breeders and genetic counselors also need this information to make informed breeding decisions that will minimize the incidence of this deleterious disorder. Concrete evidence of a genetic basis for hypoadrenocorticism is crucial to the selection of future breeding animals.

[a]SAGE. *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.

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