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# Inheritance of Urinary Calculi in the Dalmatian

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Dalmatians are unique among dogs in that they excrete uric acid in their urine as the end product of purine metabolism rather than allantoin as do other breeds of dogs. Urinary calculi form from urate (salts of uric acid) and can cause urethral obstruction in male Dalmatians. Although all Dalmatians have the primary defect, only a subset develops clinical disease. We postulated that calculi formation might have a genetic component that segregates within the breed, causing some animals to form calculi and others to never form calculi despite excreting uric acid in their urine. We used a survey to ascertain the urinary calculi status based on clinical signs of adult Dalmatians aged 6 years or older, and we used pedigrees from these same animals to estimate the heritability of the clinical manifestation of urate calculi within the breed to be .87 (.75–.96). The prevalence of the disease was 34% (24.99–43.70%) among male Dalmatians in our survey. The high heritability of the disease makes it possible for breeders to effectively select against the disease.

**Key words:** Canine; Dog; Genetic; Heritability; Inherited.

Dalmatians have a well-described change in purine metabolism that leads to the excretion of urate (salts of uric acid) in the urine rather than the excretion of allantoin like most other breeds of dogs.[1] This relative hyperuricosuria is also seen in humans and some great apes who lack the enzyme uricase. The molecular nature of the defect that causes hyperuricosuria in Dalmatians has not been determined, but experiments have shown that Dalmatians have uricase enzyme activity present in their livers.[2]

The mode of inheritance of the hyperuricosuria was analyzed by crossing Dalmatians to other canine breeds.[3,4] The puppies produced in these crosses had normal uric acid excretion in their urine consistent with a recessively inherited disorder. The trait is fixed within the breed because all purebred Dalmatians that are tested excrete higher amounts of urate in their urine than do normal dogs. Uric acid is poorly soluble in urine, and the clinical consequence of excreting large amounts of urate in the urine is a higher incidence of urate calculi (stones) than found in other breeds.[5] Calculi composed of urate can cause urethral blockage in male Dalmatians. The average age of onset of clinical signs caused by stone formation, including hematuria, stranguria, and pollakiuria, is 4.5 years.[5–7]

Two remarkable observations on calculi formation in Dalmatians are that not all Dalmatians form calculi and that 97% of Dalmatians with stones composed of salts of uric acid are male.[5] This result is surprising because all Dalmatians tested have the hyperuricosuria defect. One explanation for the reason why not all Dalmatians show clinical signs of the disease is that an inherited factor segregates within the breed and causes a subset of the dogs to form calculi. If this genetic factor were X-linked, it could explain the higher numbers of affected males than females. Alternatively, the predominance of affected males could be caused by a difference in the size of the urethra between males and females. In particular, the os penis of the male dog limits the size of the male urethra. However, females of other breeds show clinical signs when they have urinary calculi; therefore, the presence of stones in female Dalmatians may occur but go unnoticed. An alternative explanation is that calculi formation within the breed is caused by differences in husbandry or other environmental factors.

The objective of the present study was to confirm and characterize a genetic component to urinary calculi in the Dalmatian breed based on the clinical signs of this disease. This disease would be difficult to study with controlled breeding experiments because it has a late age of onset (average age 4.69 years[5]) and there may be a strong environmental component to disease manifestation. Rather, we chose to take advantage of the Dalmatians already produced by breeders to investigate a genetic component of the disease. To do so, we solicited pedigrees and disease status from the owners of Dalmatians by an online survey. Specifically, we hoped to quantify the inheritance of this disorder by the estimation of heritability with a threshold model. Heritability is a measure of the genetic similarity between parents and offspring for the trait under investigation, which, in this case, was clinical signs of urate calculi.[7] Ranging from 0 (no genetic resemblance between parents and offspring) to 1 (identical resemblance), heritability also provides a means of assessing the likely success of a breeding program intended to reduce the prevalence of calculi in Dalmatians. A threshold model is a necessary element of this analysis because of the binary nature of the phenotype of urinary calculi (ie, presence or absence). As such, our analysis must address and accommodate the obvious nonnormality found in the distribution of phenotypes. The threshold model is the most commonly used and most powerful approach to assessing inheritance in binary characters.[7] After estimating the heritability, we intended to search for evidence of a segregating locus of large effect on urinary calculi by means of complex segregation analysis.[7] This technique has long been used by geneticists to assess alternative modes of disease inheritance in humans, and we hoped to determine if the presence of urinary calculi could be explained by the action of a single locus.

## Materials and Methods

Phenotypic information was collected from Dalmatian owners by a survey available on the World Wide Web. Participants in the survey

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were recruited by an article placed in the Dalmatian Club of America magazine (*The Spotter*) and by the authors' notification of the study to regional Dalmatian clubs. Survey questions included baseline data of date of birth, gender, and spay or neuter status, as well as the American Kennel Club (AKC) registration numbers and parents' registered names. The survey was constructed to encourage an accurate assessment of urinary calculi status by asking a series of questions about the treatment and outcome of the disease, including whether the stones were removed (either surgically or by other methods) or left in the bladder. Dogs were counted as affected based on the owners' responses to the questionnaire. Information was collected on dogs that were older than 6 years of age to allow expression of the phenotype. Owners were asked if their dogs had crystals in their urine as a separate question from the question of urinary calculi because, in the author's experience (GVL), many Dalmatian owners inaccurately equate crystalluria with urinary calculi.

Prevalence of calculi in Dalmatian patients of the Veterinary Medical Teaching Hospital (VMTH), University of California–Davis, was determined by reviewing records of all Dalmatians seen at the hospital from 1985 to 2001. Dogs were counted as affected if they had a history of stone disease or if a diagnosis of stone disease was made at the VMTH.

The estimation of heritability, as well as the subsequent complex segregation analysis, is based on a set of Dalmatians with a recorded urinary calculi phenotype. The form of this phenotype is binary (ie, affected versus unaffected). Owners of 179 dogs participated in the project by submitting completed online surveys. In addition to the 179 dogs with a known phenotype, 562 relatives of these dogs (without a known diagnosis of urinary calculi) were entered into the analysis for a total of 741 dogs in the data set. Pedigrees were purchased online through the AKC to establish relationships among the animals for which we had phenotypic data. Along with the diagnosis, a variety of additional information about the amount of water consumed daily by the dogs and the time periods when the dogs were allowed access to water and urination sites was collected to identify environmental factors shared among affected dogs. Owners were asked if their dogs slept inside, had free access to water during the day and night, were allowed to urinate outside during the day and night, and if the owners perceived that their dogs drank a lot of water.

Estimation of heritability is conducted with threshold models,[8] an approach typical for binary and ordered categorical traits. The observation of urinary calculi is considered as a binary trait as $y_{ij}$ ($y_{ij} = 0$ when unaffected; 1 when affected) for the *j*-th dog ($j = 1, 2, \ldots, 179$) of the *i*-th sex ($i = 1$ for males; 2 for females). The assumption of threshold models is such that this categorical phenotype is assumed to be related to an underlying, unobservable continuous variate $\theta$ through a set of 3 fixed thresholds [$\tau_0 = -\infty$; $\tau_1 = 0$; $\tau_2 = \infty$]. Note that $\tau_1$ is set to 0 for computational convenience, with no loss in generality or affect on subsequent data analysis.

The model for $\theta$ is similar to any we might use for continuous phenotypes. The algebraic form of the model is

$$\theta_{ijk} = \mu + \text{sex}_i + \text{sleep}_j + a_k + e_{ijk} \quad (1)$$

where $\theta_{ijk}$ is an unobservable continuous variate for the *k*-th ($k = 1, 2, \ldots, 179$) dog of the *i*-th sex ($i = 1$ for male; 2 for female) in the *j*-th class for sleeping in the house ($j = 1$ for yes; 2 for no). The $\mu$ is an unknown constant, $\text{sex}_i$ is the contribution of the *i*-th sex to the expression of urinary calculi, $\text{sleep}_j$ is the potential effect of sleeping in the house on the expression of urinary calculi, $a_k$ is the additive genetic contribution of the *k*-th animal, and $e_{ijk}$ is an unknown residual. Both $a_k$ and $e_{ijk}$ are assumed to be random effects with 0 means and variances $\sigma_a^2$ (the additive genetic variance) and $\sigma_e^2$ (the residual variance), respectively. The random animal effect accounts for the covariance in phenotype of relatives and is assumed to be multivariately normally distributed, with a covariance structure based upon the additive relationships among all dogs in the data set. Because the underlying scale is unobservable, we assume that the total variance is $\sigma_P^2 = \sigma_a^2 + \sigma_e^2$ where $\sigma_e^2 = 1.0$, with no loss of generality.[9–11] Note that the heritability of urinary tract calculi, on the unobservable continuous scale, can be estimated as $h^2 = \sigma_a^2/(\sigma_a^2 + \sigma_e^2)$. Other questions from the survey also are included in the threshold model analysis, though terms for these questions are not included in model (Equation 1) in the interest of brevity. These questions address drinking habits during the day and night. Because the assumed distribution of the unobservable variate $\theta$ is normal, estimates of the effects of the ''yes'' and ''no'' replies to the questions also are normally distributed, a fact that can be used in the assessment of the significance of these replies to the presence or absence of urinary calculi.

To arrive at estimates of $\sigma_a^2$, $\sigma_e^2$, we used a mixed model Bayesian strategy outlined by Sorensen et al.[11] Estimation of the distribution of the unknown parameters uses a technique of numerical integration referred to as Gibbs sampling.[12] The algorithm is 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 are found in the analysis of this sequence of random numbers, called the Gibbs sample. Here we generated a total of 250,000 samples of possible heritability. Our estimate of heritability is taken from the mean of every 25th iterate, after discarding the first 20,000 samples, for a total 9,200 sample observations (ie, $9{,}200 = [250{,}000 - 20{,}000]/25$). The interested reader is directed to Sorensen et al[11] and to Van Tassell and Van Vleck,[13] the authors of the public domain software by which this analysis was performed, for a more complete description of the Gibbs sampling process and its theoretical justification.

To evaluate the possible segregation of a single locus with a large effect on the urinary tract calculi phenotype, we turned to regressive logistic models developed for complex segregation analysis.[14] A logistic model was used because the software for complex segregation analysis in threshold models does not exist. Commonly used in the analysis of binary disease traits, such models are built around the natural logarithm of the ratio of the marginal probabilities $\ln\{\Pr(\text{affected})/\Pr(\text{unaffected})\} = \lambda_i$ for animal *i*. With some algebraic manipulation, this leads to the expression $\Pr(\text{affected}) = e^{\lambda i}/(1 + e^{\lambda i})$ where, for animal *i*,

$$\lambda_i = \text{sex}_i + g_i + a_i + e_i \quad (2)$$

and $\text{sex}_i$ is the contribution of gender to the probability of being affected, $g_i$ is the possible contribution to disease of a major locus, $a_i$ is a polygenic contribution to disease, and $e_i$ is the residual contribution to the probability of being affected. This parameterization permits the fitting of descriptive, independent variables (equivalent to that in the analysis of variance) as well as terms for polygenic and single gene contributions. A thorough discussion of complex segregation analysis is provided by Lynch and Walsh.[15] 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[16] outline criteria that must be satisfied before acceptance of the major gene model in order to reduce the incidence of false positives. Fitting the variety of models necessary for complex segregation analysis of urinary calculi was conducted by Statistical Analysis for Genetic Epidemiology (SAGE) software.[a]

Before complex segregation analysis, SAGE requires a family structure without ''loops'' (ie, a pedigree free of inbreeding). This limitation is computational, not genetic or statistical. The 741 individual dogs were categorized into 30 distinct families of Dalmatians. However, 1 family contained 347 dogs, including several ''loops'' of inbreeding. SAGE is incapable of performing a complex segregation analysis in such a large, complex pedigree. Accordingly, this 1 actual family was reassigned into 6 separate families by ''removing'' the ancestors responsible for the inbreeding, followed by duplicating this ancestor as a ''new'' animal to create independent families. At the end of this process were 36 families that included all 179 recorded dogs, but several dogs were represented in more than 1 of the 6 ''created'' families. The impact on the final complex segregation analysis is expected to

**Table 1.** Estimates of genetic variance, heritability, and contrasts among independent variables along with their standard errors and empirical 95% confidence intervals for urinary tract calculi in Dalmatians in a threshold model.

| Question | Parameter | Mean | Standard Error | 95% Empirical Confidence Interval | |
|---|---|---|---|---|---|
| | | | | Lower Limit | Upper Limit |
| | Additive variance | 8.09 | 4.89 | 3.06 | 21.41 |
| | Heritability | 0.87 | 0.05 | 0.75 | 0.96 |
| | Males–Females | 7.06 | 2.64 | 2.60 | 13.32 |
| Sleep in house? | Yes–No | 2.25 | 1.57 | −0.48 | 5.70 |
| Out at night? | Yes–No | −2.00 | 1.37 | −5.10 | 0.37 |
| Water at night? | Yes–No | 1.20 | 1.11 | −0.83 | 3.57 |
| Out in day? | Yes–No | 1.72 | 1.08 | −0.15 | 4.15 |
| Water in day? | Yes–No | 1.80 | 2.12 | −1.84 | 6.59 |
| Drink? | Yes–No | 0.91 | 0.86 | −0.70 | 2.75 |

make the detection of a major locus more difficult, because relationships that we know exist will be lost in the analysis.

## Results

Our survey provided 179 dogs (99 males, 80 females) of known disease phenotypes, 144 dogs (80.45 ± 2.96%; percentage ± standard error) were unaffected, and 35 (19.55 ± 2.96%) were affected. Of the 35 dogs affected, 34 were males. We wished to determine if the prevalence of the disease in our survey population was similar to the disease prevalence in Dalmatians. To do this, we also estimated the disease prevalence in our hospital population from 1985 to 2001. There were 565 Dalmatians seen at the VMTH; 294 were males, of which 66 were diagnosed with urinary calculi and 12 had a history of urinary calculi. Among all observed Dalmatians, 78 of 565 (13.81 ± 1.45%) were affected, and accordingly this 95% confidence interval (CI) overlaps with that found in our survey. Among males exclusively, our survey had 34 affected dogs from a total of 99 males (ie, 34.34 ± 4.77%), where the 95% CI also overlaps the hospital sample (ie, 26.53 ± 2.57%).

A summary of the results from the analysis of the threshold model, including an estimate of the heritability of urinary tract calculi on the underlying, unobservable scale for each of the phenotypic classification schemes, is presented in Tables 1 and 2. As shown, the mean heritability of the Gibbs sample is .87, with 95% of the values ranging from .75 to .96. Evidence for the difference in the prevalence of urinary tract calculi across genders is shown in Table 1. The mean difference in genders, on the underlying scale, was estimated as 7.06 with an empirical 95% CI from 2.6 to 13.3. An interval that does not span zero (0.0) is evidence that gender differences are in the expression of urinary calculi. Conversely, as the mean estimates of the survey question effects in Table 1 indicate, all these have CIs that overlap 0.0 and can therefore be considered to not have a significant contribution to urinary calculi.

The general results of the complex segregation analysis are presented in Table 2. When interpreting the results of this analysis, the form of the model is based on the cumulative logistic function. Accordingly, the parameter estimates of Table 2 would be used to compute the variate $\lambda_i$ of Equation 2, which could, if desired, be transformed to Pr(affected).[14] Although the threshold analysis considered a variety of explanatory variables, the results presented in Table 1 indicate that only gender was a significant contributor to the incidence of urinary calculi. Accordingly, the complex segregation analysis included only an effect for gender, ignoring the additional explanatory variables.

Given the strong gender differences presented in Table 1, we also considered a 2nd analysis of our data restricted only to males (ie, all female phenotypes were recoded as unknown). It has been suggested that differences in the female urethra allow for the passage of stones, and we wanted

**Table 2.** Parameter estimates (± SE) for a complex segregation analysis in a logistic model of urinary tract calculi in Dalmatians in both a no major locus model and a general major locus model with Mendelian transmission.[a]

| | No Major Locus Model | | 95% CI | | General Major Locus Model | | 95% CI | |
|---|---|---|---|---|---|---|---|---|
| | Estimate | SE | Lower Limit | Upper Limit | Estimate | SE | Lower Limit | Upper Limit |
| Pooled susceptibility | −15.19 | 13.10 | −40.87 | 10.49 | NA | | | |
| Covariate: Sex | −28.96 | 25.29 | −78.53 | 20.61 | −76.99 | 50.33 | −175.64 | 21.66 |
| AA susceptibility | NA | | | | −79.84 | 65.50 | −208.22 | 48.54 |
| AB susceptibility | NA | | | | −1.23 | 4.16 | −9.38 | 6.92 |
| BB susceptibility | NA | | | | −64.20 | 67.95 | −197.38 | 68.98 |
| Parent–offspring covariance[b] | 0.05 | 2.37 | −4.60 | 4.70 | −0.83 | 2.71 | −6.14 | 4.48 |
| Frequency (A) | NA | | | | 0.37 | 0.41 | −0.43 | 1.17 |
| Ln (likelihood) | −22.74 | | | | −22.34 | | | |

[a] SE, standard error; CI, confidence interval; NA, not applicable.

[b] Parent–offspring covariance is a term to accommodate residual polygenic variation.

**Table 3.** Estimates of genetic variance, heritability, and contrasts among independent variables along with their standard errors and empirical 95% confidence intervals for urinary tract calculi in Dalmatians in a threshold model where all females are recorded with a phenotype of unknown.

| Question | Parameter | Mean | Standard Error | 95% Empirical Confidence Interval | |
|---|---|---|---|---|---|
| | | | | Lower Limit | Upper Limit |
| | Additive variance | 6.74 | 5.01 | 2.09 | 19.15 |
| | Heritability | 0.84 | 0.07 | 0.68 | 0.95 |
| Sleep in house? | Yes–No | −2.1 | 1.48 | −5.46 | 0.41 |
| Out at night? | Yes–No | 1.41 | 1.32 | −0.96 | 4.34 |
| Water at night? | Yes–No | −0.88 | 1.04 | −3.14 | 1.04 |
| Out in day? | Yes–No | −1.23 | 0.99 | −3.40 | 0.56 |
| Water in day? | Yes–No | −2.02 | 1.99 | −6.59 | 1.49 |
| Drink? | Yes–No | −0.35 | 0.82 | −2.01 | 1.23 |

to address the possibility that the contribution of any major gene may be more clearly expressed in males than in females. Tables 3 and 4 are a variation of the results first considered in Tables 1 and 2. However, the conclusions to be drawn from Tables 3 and 4 are no different from those to be drawn from Tables 1 and 2, specifically that the presence of urinary calculi appears to have a strong hereditary component, but there is no evidence of a segregating major locus with an affect on this binary character.

## Discussion

Reports on the inheritance of disease typically address the nature of the sampling process, usually evaluating the degree to which the sample at hand can be considered a random sample of the population of inference. Although we are concerned with the potential impact nonrandom sampling can have on the interpretation of results, we are encouraged by the similarity in the prevalence of urinary calculi among the Dalmatians in our survey and the prevalence among Dalmatian patients of the VMTH. The similarity in prevalence also lends strength to the accuracy of the phenotype data provided by owners. Although wary of the impact of ascertainment bias in our analyses, we believe our sample of dogs to be representative of the Dalmatian breed. Regardless, the impact of such sampling on the estimation of heritability is likely to be small—not large enough to alter our conclusion that the incidence of urinary calculi in Dalmatians is a trait with a strong hereditary component. In fact, a heritability of this order is suggestive, by itself, of the segregation of a single locus of large effect. Morton and MacLean[17] demonstrated that major loci tend to increase the heritability of a trait in a given population, and a value greater than .70 is comparatively large for many polygenic traits.

How these 179 dogs entered our sample is critical to the evaluation of inheritance. Most data sets in disease genetics are constructed around affected animals (ie, probands), and this set of data is no exception. However, rather than using affected dogs from the hospital population, we tried to obtain a random sample of Dalmatians by asking for information on all Dalmatians and not just Dalmatians with clinical signs of urinary calculi. Our survey was called the ''Dalmatian Survey'' rather than a ''stone survey'' to attract a more random sample of participants. One caveat of the survey approach for phenotype data is that it is possible that Dalmatians can have urinary calculi without displaying clinical signs. If this is the case, then our analysis has identified the genetic influence on the manifestation of the disease rather than calculi formation.

This sampling strategy makes correction for ascertainment bias problematic. In the estimation of heritability, it is important to note that mixed linear models are capable of accommodating nonrandomly sampled data.[18] Accordingly, the estimation of the heritability of urinary tract calculi should not be biased by family selection, provided the dogs at the base of the pedigree (dogs with no parents identified) can be considered a random sample of Dalmatians. There is no obvious test for this assumption because the dogs at the base of the pedigree have no recorded urinary calculi phenotype.

As our threshold analysis indicates, we also can confirm the well-known observation of a strong gender effect. No evidence of a major locus was identified when only males were given a recorded phenotype, indicating that an X-linked mode of inheritance is an unlikely explanation for the gender effect. It is difficult to imagine environmental factors that would produce the strong gender effect, and, consequently, we are left with the conclusion that males show clinical signs based on their urethral anatomy.

Surprisingly, none of the questions asked regarding the husbandry of animals in their home provided a significant explanation for the production of urinary calculi. Our hope had been that knowledge of such environmental factors thought to contribute to the production of urinary calculi would help us uncover the contributions of a segregating major locus. However, complex segregation analysis failed to provide statistical evidence of a major locus, just as the environmental factors included in our survey failed to explain variation in observations of urinary calculi. An important environmental factor that we did not address in this analysis is the effect of diet on urinary calculi formation.

Our estimates of the prevalence of clinical disease in male Dalmatians range from 26.53 to 34.34%. The importance of this disease to the health of Dalmatians should not be underestimated. As a result of this initial evaluation of the inheritance of the clinical signs of urinary calculi in Dalmatians, we conclude that, given the magnitude of the heritability estimate, selection against this trait should be highly successful.

**Table 4.** Parameter estimates (± SE) for a complex segregation analysis in a logistic model of urinary tract calculi in Dalmatians in both a no major locus model and a general major locus model with Mendelian transmission where all females are recorded with a phenotype of unknown.[a]

| | No Major Locus Model | | 95% CI | | General Major Locus Model | | 95% CI | |
|---|---|---|---|---|---|---|---|---|
| | Estimate | SE | Lower Limit | Upper Limit | Estimate | SE | Lower Limit | Upper Limit |
| Pooled susceptibility | −0.19 | 0.35 | −0.88 | 0.50 | NA | | | |
| AA susceptibility | NA | | | | −36.98 | 24.18 | −84.37 | 10.41 |
| AB susceptibility | NA | | | | −38.93 | 22.46 | −82.95 | 5.09 |
| BB susceptibility | NA | | | | 42.84 | 38.11 | −31.86 | 117.54 |
| Parent–offspring covariance[b] | 0.06 | 2.42 | −4.68 | 4.80 | −0.94 | 3.31 | −7.43 | 5.55 |
| Frequency (A) | NA | | | | 0.32 | 0.52 | −0.70 | 1.34 |
| Ln (likelihood) | −23.18 | | | | −22.14 | | | |

[a] SE, standard error; CI, confidence interval; NA, not applicable.
[b] Parent–offspring covariance is a term to accommodate residual polygenic variation.

This advice may be quite difficult to put into practice because of the possibility of late onset of clinical signs secondary to urinary calculi, a time that may well come after breeding decisions have been made. A screening test for urinary calculi would be very useful in this breed because it would be important to identify dogs at risk for obstruction as well as a tool to aid in breeding decisions.

## Footnotes

[a]SAGE software, Department of Epidemiology and Biostatistics, Rammelkamp Center for Education and Research, MetroHealth Campus, Case Western Reserve University, Cleveland, OH

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