Inheritance of cataracts and primary lens luxation in Jack Russell Terriers

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Objective—To characterize heritability and mode of inheritance of cataracts and primary lens luxation in Jack Russell Terriers.

Animals—872 Jack Russell Terriers from which buccal epithelial cells were collected and phenotypes for cataracts and lens luxation were determined and an additional 1,898 Jack Russell Terriers without phenotypic information used to complete pedigree relationships and that were included in the analyses.

Procedures—Narrow-sense heritabilities and genetic correlation for cataracts and lens luxation were modeled by use of threshold analysis, whereas complex segregation analysis was used to characterize mode of inheritance. For the analyses, dogs < 6 years old, unless confirmed as having cataracts or lens luxation, were classified as an unknown phenotype. The possible involvement of an *HSF4* mutation in cataracts was determined by DNA sequencing.

Results—Cataracts and primary lens luxation were highly heritable and genetically correlated, and neither was controlled by a single gene. Cataracts were not associated with an *HSF4* mutation.

Conclusions and Clinical Relevance—Analysis of the data indicated that concerted selection against both cataracts and primary lens luxation when choosing breeding animals can be used to improve ocular health in Jack Russell Terriers. (*Am J Vet Res* 2008;69: 222–227)

Cataracts represent opacities of the ocular lens that impair vision and have the potential to result in blindness. Common causes of cataracts in dogs include inherited defects, metabolic disease (especially diabetes mellitus), anterior uveitis, senility, and nutritional imbalances. In a retrospective study[1] covering a period of 40 years, 59 breeds of dogs had a greater prevalence of cataracts than that determined for randomly bred dogs, which indicated a genetic contribution. It has been proposed that an even greater number of breeds may be affected by cataracts, with estimates as high as 97 breeds.[2,3]

Inherited cataracts develop in dogs at various ages, although generally in dogs younger than what might be considered senile or geriatric or at risk for age-related cataracts. In some breeds, dogs develop cataracts shortly after birth, whereas dogs of other breeds may not develop them until between 3 and 6 years of age.[4] Breed-related cataracts are considered to be genetically controlled, but the mode of inheritance has not been clearly defined in many of the breeds because of limited data on populations in which cataracts segregate.[5,6] It is presumed that the Bichon Frise, Boston Terrier, Cocker Spaniel, Miniature Schnauzer, and Staffordshire Bull Terrier breeds have autosomal recessive modes of inheritance for cataracts.[6-8]

The current treatment modality for cataracts in dogs is phacoemulsification. Although use of this technique has relatively high success rates, it can cause blindness or painful sequelae.[9,10] Thus, for breeds in which a known genetic contribution exists, many investigators have sought to identify the gene or genes involved in expression of cataracts.[8,11,12] A single base-pair insertion in the canine *HSF4* gene was identified as responsible for cataract formation in Boston Terriers and Staffordshire Bull Terriers, whereas a single base-pair deletion in that same gene was correlated with cataract formation in Australian Shepherds.[8] The mode of inheritance for the 2 terrier breeds is considered autosomal recessive, but it is presumed that Australian Shepherds have a dominant mode of inheritance. Variation in the mode of inheritance among breeds, even when the same gene is altered, is a critical component to localization of the genetic defect responsible for cataracts. Because

Abbreviations

CERF	Canine Eye Registration Foundation
r_g	Genetic correlation between 2 traits
r_e	Environmental correlation between 2 traits

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the mode of inheritance is incompletely defined for many breeds, the study reported here involved a pedigree analysis of cataracts in Jack Russell Terriers (now referred to as Parson Russell Terriers in the American Kennel Club registry).

Jack Russell Terriers are also prone to lens luxation, which may influence a particular dog's potential risk for complications associated with cataract treatment.[13] Displacement of a lens may be secondary to trauma or primary as a result of deterioration of the zonular fibers.[14] Similar to the situation for cataracts, lens luxation can be treated specifically by surgical removal of the displaced lens or lenses.[15] Preventing the condition by genetically selecting against animals predisposed to developing the condition would be greatly preferable. Heritability of primary lens luxation has been determined for some breeds of dogs, with the suggestion that the disorder is a simple autosomal recessive condition on the basis of studies[14,16,17] in which males and females were equally affected with a relatively narrow age of onset. In other studies,[18,19] it has been suggested that lens luxation has a dominant mode of inheritance. Although primary lens luxation is found in Jack Russell Terriers, as well as other terrier breeds,[20,21] the mode of inheritance has not been determined.

Breeders and owners have identified cataracts and primary lens luxation as conditions that represent a major impact on the health of Jack Russell Terriers. Therefore, objectives of the study reported here were to characterize the heritability and mode of inheritance of cataracts and primary lens luxation in Jack Russell Terriers. An additional objective was to determine whether the mutation associated with cataracts in Boston Terriers and Staffordshire Bull Terriers also was found in Jack Russell Terriers.

Materials and Methods

Sample population—To clarify the heritability and predict the mode of inheritance of cataracts and primary lens luxation in Jack Russell Terriers, a study was initiated in conjunction with regional and national Jack Russell Terrier clubs in the United States. Owners of Jack Russell Terriers voluntarily submitted survey questionnaires that requested registered name, sire and dam, date of birth, sex, and results of an ophthalmic evaluation provided on a CERF form. The CERF evaluation requires the use of pharmacologic mydriasis, slit-lamp biomicroscopy, and indirect ophthalmoscopy and that the evaluation be performed by a board-certified veterinary ophthalmologist. Dogs were designated as affected with cataracts or lens luxation in the database when they had clinical signs consistent with the American College of Veterinary Ophthalmologists definition of heritable cataracts or lens luxation during the CERF examination. A dog was considered unaffected with these disorders when the eyes were certified as clinically normal during the CERF examination. When dogs were examined more than once, data from the most recent examination were used. Pedigree information was obtained from American Kennel Club records. In addition to the survey data, owners submitted buccal swab specimens obtained from each dog, which were used for isolation of genomic DNA.[22] The study protocol was reviewed and approved by the Institutional Animal Care and Use Committee at the University of California, Davis.

Phenotypic data—Phenotypes for cataracts and lens luxation were determined by board-certified veterinary ophthalmologists, which enabled an accurate and repeatable assessment of ophthalmic disease. Prevalence data were collected on 872 dogs. Because of the need for pedigree information, an additional 1,898 dogs were included in the analyses. These additional dogs did not have a notation of cataracts or lens luxation in the records, but they were used to complete pedigree relationships. Of all dogs included in the analyses, 125 were inbred, with a mean inbreeding coefficient of 0.051.

No additional phenotypic information (eg, coat color) was collected in conjunction with the diagnosis of ophthalmic disease. Sex was the only additional variable included in the analysis. Because of the nature of the onset of cataracts and lens luxation, and to prevent inclusion of dogs that had not yet expressed the disorder because of age, dogs < 6 years old that were judged to be free of ophthalmic disease were included in the data analyses, but their phenotypic classification was defined as unknown. Therefore, there were 137 females > 6 years old with a recorded diagnosis of cataracts (114 unaffected and 23 affected) and 88 males > 6 years old with a recorded diagnosis of cataracts (68 unaffected and 20 affected). A diagnosis of lens luxation was recorded for 137 females (111 unaffected and 26 affected) and 80 males (62 unaffected and 18 affected) that were > 6 years of age.

Estimation of heritability and genetic correlation—For the objective of estimating the heritability of each disease, in addition to the genetic correlation between lens luxation and cataracts in Jack Russell Terriers, threshold models were used to assess the risk of disease. This method assumed that a dog could be assigned to a specific disease class (unaffected or affected) when an underlying, unobservable risk (or liability) for disease exceeded $\tau = 0$, where τ is the unobservable threshold separating unaffected and affected dogs.

For a specific disease, the unobservable liability was assumed to have a multivariate normal distribution. The correlation in liability for a given ophthalmologic disease trait of 2 dogs (i and j, respectively) was modeled by use of the following equation:

$$\rho_{ij} = (a_{ij} \bullet h^2) + (\delta_{ij} \bullet \sigma_e^2)$$

where ρ_{ij} is the correlation in liability to disease between dogs i and j; a_{ij} is the additive relationship between dogs i and j; h^2 is the narrow-sense heritability of liability to disease; δ_{ij} is the coefficient for the random nongenetic component for dogs i and j, such that δ_{ij} equals 1 if i = j and 0 for all other cases; and $\sigma_e^2 = 1 - h^2$, with no loss of generality. In addition, the effect of sex on the liability of lens luxation and cataracts was also tested through the likelihood ratio test. Heritability in the narrow sense is reported as the mean ± SEM. It is worth mentioning that the data were collected in a nonrandom manner with owners submitting information. Furthermore, the

data set was constructed around dogs in which cataracts or lens luxation was diagnosed. Such data usually require an adjustment for ascertainment bias; that was not the case for these data because the models used to estimate heritability in the study reported here accommodated nonrandomly sampled data provided that it was assumed the dogs added into the study to complete the pedigree associations were a random sample of Jack Russell Terriers.

Expansion of this single trait model to a model of 2 potentially correlated traits can be accommodated by defining the r_g and r_e between 2 traits (ie, lens luxation and cataracts). Then the correlation in liability between lens luxation and cataracts of 2 dogs (i and j, respectively) was modeled by use of the following equation:

$$\theta_{ij} = (a_{ij} \bullet r_g \bullet \rho[h_x^2 \bullet h_c^2]^{0.5}) + (\delta_{ij} \bullet r_e \bullet [\{1 - h_x^2\} \bullet \{1 - h_c^2\}]^{0.5})$$

where θ_{ij} is the correlation in liability between lens luxation and cataracts of dogs i and j. h_x^2 is the narrow-sense heritability of liability to lens luxation, and h_c^2 is the narrow-sense heritability of liability to cataracts. Accordingly, the analysis estimated the 2 unknown heritabilities (ie, h_x^2 and h_c^2) in addition to the unknown genetic correlation (ie, r_g). Calculations were implemented through a computer program.[23,a]

Complex segregation analysis—The possibility that lens luxation or cataracts in Jack Russell Terriers could be influenced by the action of a segregating locus of large effect was also examined. Complex segregation analysis[24] is intended to integrate Mendelian transmission genetics at a single locus, with the patterns of covariance expected in polygenic inheritance. Criteria to establish the necessary evidence for the acceptance of a single locus model while reducing the risk of false-positive discovery of a major locus are provided elswhere.[25] Evaluation of the models necessary for complex segregation analysis in each of these binary disease traits was conducted with a Bayesian software package[b] by analyzing 1 trait at a time. The Bayesian software was an extension of a package of subroutines for genetic analyses with Gibbs sampling[26] that was rewritten to accommodate complex segregation analysis in binary traits for pedigrees that include inbreeding. In contrast to the other computer program[a] used in our study, the Bayesian software package could not accommodate multiple-trait complex segregation analyses. Accordingly, each analysis was conducted separately for each ophthalmologic disease.

DNA sequencing—To determine whether the mutation that has been identified as being associated with primary cataracts in 2 terrier breeds was also correlated with cataracts in Jack Russell Terriers,[8] we sequenced exons 8 and 9 of *HSF4* from the genomic DNA extracted from the buccal swab specimens obtained from 2 Jack Russell Terriers that expressed cataracts by 30 months of age (affected), 1 Jack Russell Terrier known to produce offspring that developed early onset cataracts yet did not develop cataracts itself (as determined by results of CERF examination) when > 7 years old (presumed carrier), and 2 Jack Russell Terriers that had not produced any offspring that developed cataracts and were considered clinically normal during CERF examinations conducted when both dogs were ≥ 7 years old (unaffected) for use in the DNA analyses. Exons 8 and 9 were amplified by use of primers and conditions described elsewhere.[8] The amplified product was purified by use of a gel-purification kit[c] and sequenced at an automated DNA sequencing facility.[d]

Results

Estimates of heritability, r_g, r_e, and sex differences in liability to disease for each of the traits investigated were calculated. Lens luxation has a considerably (P = 0.002) large genetic component, a conclusion that was equally justifiable for cataracts, on the basis of heritability estimates of 0.99 and 0.73 for lens luxation and cataracts, respectively. Moreover, the impact of sex (dif-

Table 1—Values of model parameters for lens luxation in Jack Russell Terriers in a Bayesian mixed-inheritance model with a completely recessive major locus, with and without Mendelian transmission of the putative major allele.

Parameter	Polygenic variance	Major locus variance	Additive effect	Dominance deviation	τ_{AA}*	τ_{AB}*	τ_{BB}*	Frequency (q)
Mendelian transmission								
Mean†	1.80	4.14	2.64	–2.64	1.0	0.5	0	0.42
Mode	2.82	3.69	5.25	–1.29	—	—	—	0.40
SD	0.78	2.50	0.59	0.59	—	—	—	0.11
HDR 95%								
Low	0.06	0.51	1.10	–5.41	—	—	—	0.16
High	3.20	19.43	6.09	–0.45	—	—	—	0.89
Non-Mendelian transmission								
Mean	1.59	11.09	3.93	–3.93	0.85	0.48	0.20	0.46
Mode	2.35	0.07	11.13	–0.33	0.98	0.89	0.00	0.00
SD	0.83	10.21	1.24	1.24	0.12	0.12	0.13	0.21
HDR 95%								
Low	0.03	0.00	1.83	–9.47	0.41	0.15	0.00	0.00
High	3.22	75.23	11.37	–0.08	1.00	0.92	0.74	1.00

*Mendelian transmission parameter, which is the probability of transmitting an A allele. For Mendelian transmission, these values are fixed at 1.0, 0.5, and 0 for putative major genotypes AA, AB, and BB, respectively. Non-Mendelian transmission implies estimation of these values from the data. †Marginal posterior mean.

HDR = Highest-density region. q = Putative major locus allele frequency. — = Not applicable.

Table 2—Values of model parameters for cataracts in Jack Russell Terriers in a Bayesian mixed-inheritance model with a completely recessive major locus, with and without Mendelian transmission of the putative major allele.

Parameter	Polygenic variance	Major locus variance	Additive effect	Dominance deviation	τ_{AA}*	τ_{AB}*	τ_{BB}*	Frequency (q)
Mendelian transmission								
Mean†	1.60	5.07	2.69	–2.69	1.0	0.5	0.0	0.46
Mode	2.79	4.47	0.78	–2.63	—	—	—	0.48
SD	0.86	3.30	0.64	0.64	—	—	—	0.12
HDR 95%								
Low	0.00	0.00	0.00	–4.96	—	—	—	0.13
High	3.22	22.17	5.81	0.18	—	—	—	0.89
Non-Mendelian transmission								
Mean	1.33	16.79	5.24	–5.24	0.94	0.11	0.04	0.90
Mode	0.46	12.57	8.01	–4.06	0.95	0.07	0.04	0.29
SD	0.84	9.33	1.11	1.11	0.04	0.06	0.03	0.05
HDR 95%								
Low	0.00	0.00	3.24	–8.73	0.79	0.00	0.00	0.00
High	3.21	62.69	9.71	–2.33	1.00	0.41	0.23	1.00

See Table 1 for key.

ference between males and females) on expression of lens luxation (estimate [SE]; 0.07 [0.19]) and cataracts (0.18 [0.20]) was considered inconsequential given the magnitude of the SE (ie, estimates for the impact of sex were well within 1 SE of the value of 0). Thus, there was no differential contribution to expression of lens luxation or cataracts ($P = 0.20$) on the basis of the sex of a dog. There was a significant r_g ($r_g = 0.56$; $P = 0.01$) between lens luxation and cataracts. However, the r_g was not significantly different from 0 because the SE exceeded the point estimate and encompassed 0.

Several analyses were conducted for the complex segregation analysis of lens luxation. When only the analyses with fixed Mendelian transmission probabilities were considered, the data provided evidence for a segregating major locus (**Table 1**). Yet those results would have been misleading without consideration of the non-Mendelian transmission analysis. Thus, although estimates of the additive and dominance contributions as well as the total genetic variance contributed by the putative major locus differed significantly from 0 in the Mendelian analyses, when the probability of transmitting the putative disease allele was estimated from the data (rather than fixed at the expected Mendelian values of 1.0, 0.5, and 0), the pattern for cataracts did not readily conform to expectations of a major locus. In addressing criteria established in another study,[25] our estimates of the probabilities for allele transmission differed significantly from the expected Mendelian values of 1.0, 0.5, and 0 for transmission of the A allele from AA, AB, and BB genotypes, respectively. Specifically, the highest-density region for each of the transmission probabilities revealed considerable overlap among the 3 putative genotypes, which indicated that the transmission of this allele did not behave by the established rules put forth by Mendel. Therefore, results for the 2 analyses for transmission probabilities together cannot provide convincing evidence for the segregation of a locus with a substantially large impact on lens luxation.

A similar conclusion for cataracts was reached by use of the same criteria. In analyses with fixed Mendelian transmission probabilities, the major locus variance overlapped with 0, which indicated that there was no evidence for a major locus of large effect segregating with an influence on cataracts in Jack Russell Terriers (**Table 2**). The non-Mendelian analyses provided further support to this conclusion in that the estimation of the transmission probability for the heterozygous genotype did not overlap with the expected value of 0.5.

Table 3—Genomic sequence of *HSF4* exon 9 in a region (bp 3,627 to 3,656)[27] associated with cataracts in Staffordshire Bull Terriers (SBT), Boston Terriers (BT), and Australian Shepherds (AS) for 3 classes of Jack Russell Terriers (JRT; affected with cataracts, presumed carrier,* and unaffected) and for Boxers, which are a breed not predisposed to development of cataracts.

Category	Sequence (5′–3′)
SBT and BT affected	TTTTTGCGTGACAGCCCCCCCCCC**C**ACTGTC
AS affected	TTTTTGCGTGACAGCCCCCCCCCCACTGTC
JRT	
Affected-1	CTTCTGCGTGACAGCCCCCCCCCCACTGTC
Affected-2	CTTCTGCGTGACAGCCCCCCCCCCACTGTC
Presumed carrier*	CTTCTGCGTGACAGCCCCCCCCCCACTGTC
Unaffected-1	CTTCTGCGTGACAGCCCCCCCCCCACTGTC
Unaffected-2	CTTCTGCGTGACAGCCCCCCCCCCACTGTC
Boxer	TTTTTGCGTGACAGCCCCCCCCCCACTGTC

An insertion is indicated by bold and underline, whereas a conserved mutation is indicated by underline alone.

*Produced offspring that developed early onset cataracts yet did not develop cataracts itself (as determined by results of CERF examination) when > 7 years old.

Although the data did not support a segregating major locus, they did reveal a significant genetic contribution to cataracts. An insertion in exon 9 of *HSF4* has been associated with presumed autosomal recessive cataracts in 2 terrier breeds. To determine whether that same mutation was directly correlated with cataracts in Jack Russell Terriers, exon 9 was sequenced in affected dogs, a dog that had produced offspring that developed cataracts yet that did not develop cataracts itself, and unaffected dogs. The sequence data for all 3 classes of dogs were identical, which indicated that the putative mutation responsible for cataracts in Boston Terriers and Staffordshire Bull Terriers was not detected in Jack Russell Terriers (**Table 3**). Furthermore, no deletions in exon 9 were detected in any of the 3 categories of Jack Russell Terriers, thus ruling out the mutation identified as associated with cataracts in Australian Shepherds.[8] Two conservative DNA substitutions immediately outside the mutated region were detected in all Jack Russell

Terriers that were not detected for reference Boxers,[27] Boston Terriers, Staffordshire Bull Terriers, or Australian Shepherds.

Discussion

Similar to results reported for other breeds, cataracts and lens luxation in Jack Russell Terriers had a substantial genetic component and were not influenced by sex. The exceedingly high heritability estimate for lens luxation must be viewed with caution. Values of heritability in excess of 0.90 are certainly not routinely detected. The possibility exists that the combination of a discrete trait and recorded patterns of inbreeding may have led to an estimate near the theoretic boundary of 1.0.

In the study of Jack Russell Terriers reported here, lens luxation and cataracts were positively, genetically correlated with each other. This implies that selection criteria applied to reduce the incidence of condition should also benefit reduction of the incidence for the other condition. In other studies,[28-30] investigators have found other concurrent ocular disorders, such as microphthalmia, in association with presumed inherited cataracts. Those findings of genetic association among various ocular disorders, coupled with the data reported here, suggest that real progress can be made toward improvements in ocular health.

Although the major locus model for lens luxation and cataracts must be rejected because the estimates of allele transmission failed to conform to Mendelian patterns of inheritance as evidenced by the large overlapping highest-density region for the 3 putative genotypes, which thereby indicated that criteria for a major locus have not been met,[25] the criteria also have not been violated. Thus, although the major locus model must be rejected with the data reported here, additional data may modify that conclusion if the additional data points reduce variation of the parameter estimates.

An insertion that introduces an early stop codon in the *HSF4* gene has been implicated in the development of cataracts in Boston Terriers and Staffordshire Bull Terriers. A deletion in the same region of the *HSF4* exon 9 also introduces an early stop codon and is associated with cataracts in Australian Shepherds, with affected dogs being heterozygous or homozygous for the mutation, which is suggestive of an autosomal dominant mode of inheritance.[8] Comparing the sequence of exon 9 of the *HSF4* gene for cataractous Jack Russell Terriers with the DNA sequence in Staffordshire Bull Terriers and Boston Terriers was reasonable, and lack of a causal mutation in the Jack Russell Terriers was not surprising. The lack of statistical support for the existence of a major locus affecting expression of cataracts in Jack Russell Terriers made the existence of a single causal mutation improbable. The ancestral history of Staffordshire Bull Terriers is similar to that of Boston Terriers, with both considered to have been derived from Bull Terriers during the late 1800s.[31,32] In contrast, Jack Russell Terriers are considered to have been derived from Fox Terriers.[33] Furthermore, cluster analysis reveals that terriers, as a group, are quite diverse in terms of their genetic ancestry,[34] which implies that common causal mutations may be rare among terrier breeds. The complex mode of inheritance possibly aligns cataracts of Jack Russell Terriers with 2 other breeds that have inherited cataracts (ie, German Shepherd Dogs and Cocker Spaniels), both of which lack mutations in this gene.[8]

In the study reported here, we ascertained that cataracts and lens luxation were both characterized as highly heritable in Jack Russell Terriers. Moreover, we concluded that the pattern of inheritance for these 2 ocular disorders is polygenic, with no convincing evidence that a major locus of large effect contributes to the expression of either disorder. The 2 ocular disorders were genetically correlated, which indicated that the genetic liability for cataracts is associated with the risk for lens luxation. Considered together, these findings can be used as encouragement for breeders because the high heritabilities suggest that selection against these diseases will be quickly rewarded with improvements in ocular health. Moreover, there was a positive r_g. Had a strong negative correlation been uncovered, breeders would have been forced to confront the unsettling genetic conclusion that selection against 1 ocular disease would lead to an increase in the liability of the other. Instead, the recommendation is that breeders must remain vigilant for both disorders when choosing the sires and dams of future generations of Jack Russell Terriers.

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