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Age of neutering contributes to risk of cruciate ligament rupture in Labrador Retrievers

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OBJECTIVE
Cruciate ligament rupture (CR) in Labrador Retrievers is a complex polygenic disease with high heritability. The environmental contribution to CR risk remains poorly characterized. An accurate genetic risk test for CR in the Labrador Retriever has been developed. This enables evaluation of environmental risk with knowledge of genetic disease predisposition through study of dogs with phenotypic disease status that is discordant with their genetic risk. The objective of this study was to identify environmental factors that contribute to CR in Labrador Retrievers through evaluation of dogs with clinical phenotypes that are discordantly predicted with the use of genetic markers.

METHODS
Dogs were prospectively recruited between January 2013 and December 2022. To study discordant subjects, case dogs with a posterior risk probability value < 0.75 and control dogs with a posterior risk probability of > 0.25, determined with the use of an average of 8 statistical models, were selected. The environmental factors investigated were neuter status, age of neuter, withers height measured at the dorsal-most ridge between the scapulae, weight, body mass index, and athletic activity.

RESULTS
Ninety three dogs were discordant: 58 dogs were discordant CR cases, and 35 dogs were discordant CR controls. Neutering before 12 months of age was a significant risk factor for CR development. Sex, neuter status, or status as an athlete was not associated with CR risk.

CONCLUSIONS
Neutering before 12 months of age influences risk of CR in Labrador Retrievers.

CLINICAL RELEVANCE
This information can inform management decisions about Labrador Retrievers regarding age of neutering, body condition, and athletic activity. The primary factor influencing CR development in Labrador Retrievers is polygenic intrinsic genetic risk.

Keywords: cruciate, Labrador Retriever, environmental, genetic, discordant

Non-contact cruciate ligament rupture (CR) is a frequently diagnosed degenerative condition of the canine stifle responsible for approximately 20% of canine lameness and results in a substantial financial burden to the public.[1] Cruciate ligament rupture is a complex genetic disease under the control of both environmental and genetic risk factors.[2–10] It is recognized that breed is the most impactful risk factor for disease development.[11,12] Other previously reported environmental risk factors include body weight, body condition, neuter status, and activity, although results between studies are inconsistent.[4,10–13]

Labrador Retrievers are an overrepresented breed for CR, with a prevalence of 5.79%.[11] In Labrador Retrievers, CR is a highly polygenic complex genetic disease with both genetic and environmental risk factors contributing to disease risk.[2,3,12,14–16] Heritability estimates of Labrador Retriever CR range from 0.54 to 0.89, indicating that the disease has high heritability.[5,14]

A recently developed genetic risk test for CR in Labrador Retrievers is approximately 98% accurate for prediction of non-contact CR case-control status in the Labrador Retriever using 10-fold cross validation in a large reference population. In this model, the posterior

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probability (PP) threshold for prediction of case CR status is > 0.5 **(Figure 1)**.[17] As a complex polygenic trait, genetic risk testing will not reach 100% accuracy due to environmental influences on disease risk. The influence of environmental factors is particularly impactful in those dogs for which genetic risk scoring incorrectly predicts case-control disease status and can help gain insight into significant environmental factors that could be modified for dogs deemed to be at high risk because of genetic predisposition.

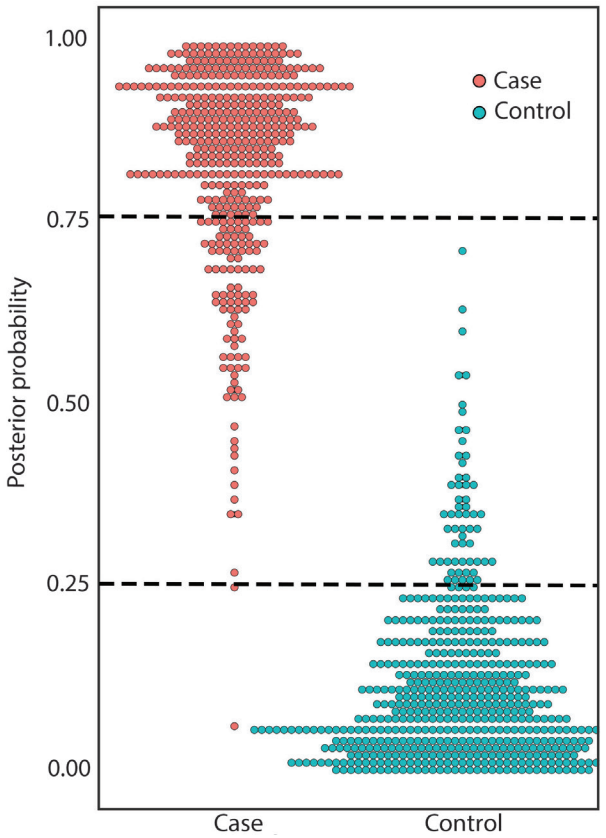

Figure 1—A plot of the posterior probability for genetic risk of cruciate ligament rupture (CR). Ten-fold cross-validation results for 710 Labrador Retrievers recruited at the University of Wisconsin-Madison were studied. Discordant CR cases were considered dogs that had posterior probability for CR development < 0.75 (n = 58), and discordant CR controls were dogs that had posterior probability for CR development > 0.25 (n = 35). These cutoff values are represented by the horizontal dotted lines, and each dog is represented by a red (case) or blue (control) dot.

The objective of this study was to identify environmental risk factors that contribute to development of CR in Labrador Retrievers through evaluation of dogs with clinical phenotypes that are discordant with their genetic risk assessment. We investigated the influence of neuter status, age of neuter, withers height at the dorsal-most ridge between the scapulae, weight, body mass index (BMI), and athletic activity in dogs with discordant findings between phenotype and genetic risk. We hypothesized that, in Labrador Retrievers, overall neutering, neutering before 12 months of age, increased BMI, and higher athletic activity would impact CR disease status.

Methods

Client-owned purebred Labrador Retrievers were prospectively recruited between January 2013 and December 2022 by the Comparative Genetics and Orthopedic Research Laboratory at the University of Wisconsin (UW)-Madison from the UW-Madison Veterinary Care Hospital and through online outreach. Permission was obtained from all owners. All procedures were undertaken in accordance with the Guide for the Care and Use of Laboratory Animals with approval from the IACUC at UW-Madison's School of Veterinary Medicine (V005453).

Dog CR disease status was determined by a board-certified small animal surgeon through either orthogonal or standing lateral stifle radiographs. A patient physical examination was also undertaken for dogs recruited at the UW-Madison Veterinary Care Hospital.[18] Affected dogs had radiographic evidence of CR including stifle effusion and osteophytosis with physical examination findings indicative of stifle laxity due to CR.[18] Control dogs were 8 years of age or older, with normal stifle radiographs and normal stifles on orthopedic examination. Dogs were excluded if they had a history of stifle trauma, immune-mediated polyarthritis, hyperadrenocorticism, or a history of steroid administration.

Demographic data, including weight, withers height, sex, and neuter status were collected; age of neutering and information on athletic activity were also obtained by means of an owner questionnaire. Age of neutering was binned into 3 categories: < 6 months, 6 to 12 months, and > 12 months. Dogs were categorized as either athletic or not athletic on the basis of owner reporting; to be considered athletic, dogs had to participate in activities such as hunting, agility, field trials, or tracking with a minimum frequency of once a week. Body mass index was calculated using body weight and withers height, as follows: ([weight (kg)]/[withers height (m)]^2).[19]

Blood or saliva was collected for DNA isolation. Dogs were genotyped with the CanineHD BeadChip (Illumina Inc), which contained approximately 230,000 single nucleotide polymorphisms (SNPs) distributed across the canine genome (UU_Cfam_GSD_1.0/canfam4). Polygenic risk score prediction was undertaken with the use of 4 Bayesian (Bayesian Lasso, BayesB, BayesC, and Bayesian Ridge Regression) and 4 machine learning models (Random Forest, Support Vector Machine, Lasso, and Gradient Boosting)[20,21] with a reference population of 1,006 Labrador Retrievers genotyped and phenotyped for non-contact CR.[16] A 10-fold cross-validation procedure using 2% of top genome-wide association SNPs was used. To select the optimum number of the top SNPs for fitting the prediction models, a grid search was conducted and the model evaluated across different percentages of SNP sets. The models were evaluated with the R^2 metric. For each dog, the PP for risk of being a case was obtained. We considered

a PP threshold of 0.50 to distinguish cases from controls. Thus, to establish PRS prediction of disease, dogs having a PP ≥ 0.5 were considered to have high intrinsic genetic risk of CR development and dogs having a PP < 0.5 were considered to have low intrinsic genetic risk of CR (Figure 1).

For this study, dogs with genetic risk assessment that did not correlate with their clinical phenotype were considered discordant dogs. For CR cases, this included dogs with a PP < 0.75, and for CR controls this included dogs with a PP > 0.25 (Figure 1).

Statistical analysis

Statistical analysis was performed with Prism (version 10.1.1; GraphPad Inc) or R.[22] Data are reported as mean ± SD. Categorical covariables including sex, neuter status, age at neuter, and athletic activity were analyzed between discordant cases and discordant controls with a Fisher's exact test. Odds ratios were calculated from 2 X 2 contingency tables. Continuous variables, including height, weight, and BMI, were tested for normality with the D'Agostino and Pearson test. All groups were normally distributed and thus analyzed with a Student's *t* test. Results with $P < .05$ were considered significant.

Results

Seven hundred ten dogs recruited at UW-Madison were included in the reference population for this study, including 318 cases and 392 controls. The remaining dogs were recruited at Cornell University with more limited phenotyping. Ninety-three dogs were identified as discordant. Of these, 58 dogs were discordant CR cases, including 6 intact males, 24 castrated males, 2 intact females, and 26 ovariectomized females; 35 dogs were discordant CR controls, including 8 intact males, 11 castrated males, 2 intact females, and 14 ovariectomized females. Weight was recorded for 54 of 58 (93%) discordant CR cases and 32 of 35 (91%) discordant CR controls. The age range of neutering was known for 17 of 52 (32%) neutered discordant CR cases, including 5 neutered before 6 months of age, 8 neutered between 6 and 12 months of age, and 4 neutered after 12 months of age. Age of neutering was known for 9 of 26 (35%) discordant CR controls, including 2 neutered between 6 and 12 months of age and 7 neutered after 12 months of age. Athletic status was known for 18 discordant cases, of which 8 were considered athletic. Athletic status was known for 8 discordant controls, of which 4 were considered athletic. Withers height was known for 30 of 58 (52%) discordant CR cases and 15 of 35 (43%) discordant CR controls.

Categorical data, including age of neutering, neuter status, sex, and athletic status were analyzed between groups. Risk of CR was increased in dogs neutered before 12 months of age (OR = 11.38; $P = .01$). Neutering before 6 months of age was not a significant factor ($P = .17$), nor was neutering between 6 and 12 months of age (OR = 3.11; $P = .23$). Overall neutering was also not a risk factor (OR = 1.8; $P = .27$). There was no association with risk groups with regard to sex ($P = .83$), neuter status in males ($P = .11$), neuter status in females ($P = .61$), or status as an athlete ($P > .99$).

Quantitative data, including weight, height, and BMI, were analyzed between groups. No differences were seen between groups for weight ($P = .18$), height ($P = .34$), or BMI ($P = .43$; **Table 1**).

Table 1—Summary of categorical and continuous variables in discordant cruciate ligament rupture cases (n = 58) and discordant cruciate ligament rupture controls (n = 35).

	Discordant cases	Discordant controls	*P* value
Weight (kg)	35.58 ± 6.92 (n = 54)	33.49 ± 7.21 (n = 32)	.18
Height (m)	0.59 ± 0.04 (n = 30)	0.58 ± 0.05 (n = 15)	.34
BMI (kg/m^2)	98.63 ± 19.29 (n = 29)	103.5 ± 19.72 (n = 15)	.43

Data are reported as mean ± SD.
BMI = Body mass index.

Discussion

We evaluated environmental risk factors for CR in Labrador Retrievers that either developed CR despite low genetic risk or that did not develop CR despite high genetic risk. As CR is a complex genetic disease with high heritability in the Labrador Retriever,[5,14] environmental risk factors can be challenging to study. This was the first study undertaken of dogs in which knowledge of genetic risk was used to enable identification of influential and nonsignificant environmental factors contributing to disease development. The ability to undertake accurate polygenic risk score prediction of CR in Labrador Retrievers establishes the substantial influence of genetic risk on development of CR.[17] While there have been previous studies of risk factors for CR in dogs, the present study is the first to focus specifically on environmental risk with knowledge of background genetic risk in a single breed, the Labrador Retriever. Polygenic risk score assessment designed with a Labrador Retriever reference population does not accurately predict other breeds.[17] Cruciate ligament rupture is a heterogenous and complex disease across breeds as evidenced by its variable breed-dependent heritability.[5,8,14]

We had hypothesized that neuter status, age of neutering, BMI, and athletic activity would influence CR risk in Labrador Retrievers. We partially accepted this hypothesis, as neutering before 12 months of age was a significant environmental risk factor for CR in Labrador Retrievers. However, overall neuter status and neutering before 6 months of age were not significant factors influencing risk of CR. This finding concurs with other investigations looking at age of neutering relative to disease occurrence where, when age of neutering is significant within a given breed and sex, neutering before 12 months of age is associated with greater risk of CR development, while overall neuter

status is less impactful.[9,13,16,23,24] In agility dogs, CR is more commonly seen in females neutered before their first heat cycle and males neutered before 10 months of age.[25] The overall effect of neutering on risk of CR across all dog breeds is unclear. Studies investigating CR risk in diverse dog populations have shown both an increased risk of disease in neutered dogs and a lack of difference in risk between neutered and intact dogs.[26,27] It is recognized that breed is impactful with regard to whether neutering affects risk of CR disease development.[4,13,16,23,24] These differences across studies are likely associated with the specific demographics of the populations studied.

Our study did not find sex to be an influential factor for disease risk in Labrador Retrievers. Studies investigating CR risk in individual breeds indicate that the impact of sex on disease risk is breed dependent.[9,13,23] It is for this reason that results from studies using mixed dog populations are inconsistent with regard to the effect of sex on disease risk.[4,9,10,13,16,23,24,27–32]

The pathophysiology behind the role of neutering on CR risk in dogs is not known. Sex hormones influence risk of anterior cruciate ligament (ACL) rupture in humans, in which it is well established that females, particularly adolescents, experience ACL rupture at a higher rate than their male counterparts.[33] This correlates to findings associating alterations in sex hormone status from neutering with an increased risk of CR in dogs. Like in dogs, the pathophysiology behind this increased risk in humans is not understood,[34] although rupture risk in humans, like dogs, is highly heritable.[35]

We did not find an association between participation in athletic activity and CR in this study. Little is known about the beneficial or detrimental relationship between athletic activity and CR, although flyball and agility have been implicated in risk.[10] Notably, in the present study, athletic activity was owner reported and specific activities that dogs participated in were not recorded. In human athletes, participation in a subset of sports, such as gymnastics and soccer, is related to increased risk of ACL rupture.[36,37] The high-impact rotational landing movements seen in these sports are similar to those of canine athletes participating in activities such as flyball and agility work, which contribute to CR development.

We did not find that height, weight, or BMI contributes to CR risk in the Labrador Retriever. Earlier studies[29,32] have found increased weight to associate with CR risk, although these studies evaluated a mixed-breed population, and thus the relationship between weight and CR could be impacted by weight differences between at-risk and protected breeds. Risk of CR has also been associated with increasing BMI, as determined through height and weight ratios. However, it is again notable that these studies also have a mixed population of dogs, leading to the possibility that differences in breed morphology could be a contributing factor.[10,27,29,31]

This study had several limitations. A total of 93 dogs were used for this study, although all phenotypes evaluated were not available for all dogs. Results were limited by sample size for some analyses, and future work with an increased sample size would be of value. In addition, data on athletic activity were collected from a self-reported owner survey, which may have introduced bias. It is important to note that, due to significant genetic heterogeneity between breeds, findings in this Labrador Retriever study may not translate to other breeds.

In conclusion, of the environmental variables evaluated, neutering before 12 months of age significantly increased risk of CR development in Labrador Retrievers, but body condition and athletic activity did not. Neutering is an important and modifiable risk factor that has been provisionally implicated as an environmental risk factor in an earlier genetics study.[38] The results of this work further affirm that CR in the Labrador breed is highly influenced by genetics.[2,3,5,14,15] These results inform veterinarians and owners concerned about management of CR risk in their patients, particularly those that have a higher genetic risk of CR.

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