PURINA PRO PLAN

LABRADOR RETRIEVER Update

A NESTLÉ PURINA PUBLICATION DEDICATED TO LABRADOR RETRIEVER ENTHUSIASTS

VOLUME 17 | FALL 2019

EPILEPSY RESEARCH

Genetics & Innovative Treatments Are Key

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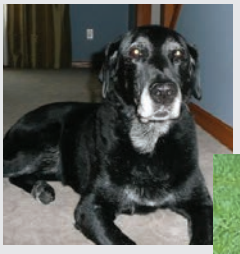
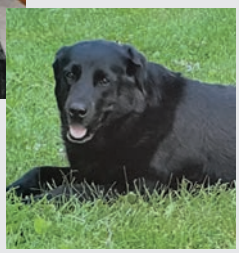
LABRADOR RETRIEVERS MAY BENEFIT FROM

EPILEPSY RESEARCH TO IDENTIFY GENETIC RISK FACTORS



"Ebony"



"Lilly"

Joe Solheid of Eden Prairie, Minnesota, adores black Labrador Retrievers.

His first one, named "Ebony," was an energetic hunting companion who loved to retrieve. His current black Labrador, named "Lilly," almost 8 years old, is a beloved family pet and companion.

Ebony and Lilly were bred by different breeders. Their pedigrees have no common relatives, yet they both developed a common canine disease: epilepsy.

"When Lilly was about 6 months old, she started having seizures every two to three weeks," Solheid says. "We couldn't come up with a trigger. There were no cases of epilepsy in her bloodline up to three generations back. My veterinarian, Fran Smith, is the breeder. She also treated Ebony and kept her going until she died at age 15."

A responsible breeder, Fran Smith, DVM, PhD, DACT, (Danikk Labrador Retrievers), of Lonsdale, Minnesota, takes to heart the importance of health testing breeding dogs. She is president of the Orthopedic Foundation for Animals, a non-profit organization dedicated to reducing the incidence of genetic diseases, and also is a board-certified theriogenologist.

A purebred dog enthusiast since 1956 and Labrador Retriever lover

since 1971, Dr. Smith focuses on producing multipurpose family and hunting companions with good-natured temperaments. Danikk takes pride in having produced more than 20 show champion-titled Labrador Retrievers, three Obedience Trial Champions, plus multiple working dogs that have earned Master Hunter, Senior Hunter and Junior Hunter titles.

"The source of Lilly's epilepsy is a mystery," Dr. Smith says. "There is no epilepsy in her sire's or dam's pedigrees for several generations back. My goal is to maximize the genetic advantages each parent brings to a breeding. I take cautions to prevent inherited diseases by testing for those that have been identified through DNA testing. If there is a learning here, it is that epilepsy is a complex disease that may crop up despite your best efforts."

Dr. Smith prescribed the same medications — phenobarbital and potassium bromide — to treat both dogs' epilepsy. "Ebony had fewer seizures early on but they were more severe," Solheid says. "After age 12, we took Ebony off the epilepsy medicine completely, as she had not had a seizure in six years. It was almost like she outgrew them."

Meanwhile, Lilly, whom Solheid describes as a mellow, wonderful companion, is doing well. "Her infrequent seizures occur with little forewarning," he says. "She tends to disappear into a room by herself, which is not typical behavior for her. About a year ago, we reduced the amount of potassium bromide she takes, and in another year, we may be able to cut back more if she keeps doing well."

In about 70 percent of epileptic dogs, medications work well to control the seizures. Although the drugs generally don't eliminate all seizures and there is not "one size fits all" regarding which medications work best for a specific dog, it

LABRADOR RETRIEVER OWNERS CAN CONTRIBUTE TO EPILEPSY RESEARCH

Owners of Labrador Retrievers are encouraged to participate in epilepsy research that is part of the Epilepsy Research Initiative of the AKC Canine Health Foundation. The Labrador Retriever Club is among the donors to the Epilepsy Research Initiative. Here is how you can help:

- Contribute DNA samples to participate in the genetic research underway at the University of Missouri. Dr. Gary Johnson is studying the DNA variants of epilepsy and hopes to develop a genetic test to identify suspect variants. The team has received DNA samples from 138 breeds and from mixed breeds. Blood samples and clinical records are needed from affected dogs and their healthy relatives. For information, you may contact project coordinator Liz Hansen at HansenL@missouri.edu.
- Join the study at North Carolina State University to learn about how gastrointestinal health impacts epilepsy. Dr. Karen Muñana is seeking to enroll participants in which there are two dogs in the household — one epileptic and one unaffected. The epileptic dog must be on phenobarbital alone or no seizure medication. Both dogs must be on the same diet. To participate, owners will be asked to collect fecal samples from both dogs to ship to the investigators and answer a brief online survey. Owners will be provided the necessary supplies and prepaid shipping labels. For information, please contact study coordinator Julie Nettifee at janettif@ncsu.edu.
- Take part in a clinical trial at Colorado State University to learn about the efficacy of cannabidiol (CBD) oil for the treatment of dogs with epilepsy. Dr. Stephanie McGrath aims to enroll dogs with epilepsy that are receiving conventional anticonvulsants and having at least two seizures per month. The study covers costs related to the trial including examinations, magnetic resonance imaging, spinal tap, bloodwork, and CBD oil. An online survey can help you determine if your dog qualifies for the clinical trial. Please call 970-305-0455 or send an email to CSUNeuroTrials@colostate.edu for more information.

AKC CANINE HEALTH FOUNDATION ESTABLISHES THE EPILEPSY RESEARCH INITIATIVE

The AKC (American Kennel Club) Canine Health Foundation has contributed more than $673,000 to epilepsy research since 2017 via its Epilepsy Research Initiative. The Initiative was launched to provide funds to support innovative research that will advance understanding of the mechanisms underlying epilepsy, leading to more effective treatments, as well as to provide educational resources for dog owners and veterinarians.

Purina and the AKC Canine Health Foundation have worked together since 1997 to support canine health research to benefit all dogs.

takes time and experimentation to find the right combination and dosage of medications.

On a genetic front, research is underway to look for DNA variants in hundreds of epilepsy candidate genes that contribute to increased risk for epilepsy in dogs. Led by Gary Johnson, DVM, PhD, associate professor and molecular geneticist at the University of Missouri, the goal is to find the changes in genes that may increase the risk for epilepsy, so breeders can use these tools to help reduce the incidence of disease.

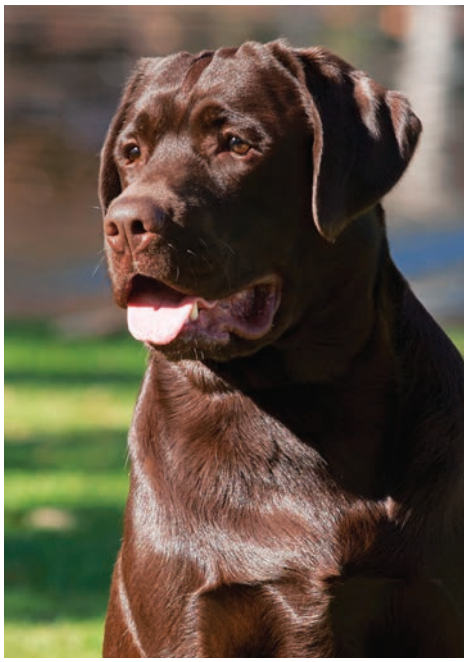
Canine epilepsy is ranked as one of the top health concerns of dog breeders and owners. Among their worries are the impact of seizure frequency and severity on a dog's quality of life and possible complications from the side effects of medications. They anguish whether epilepsy could shorten their dog's life.

Although epilepsy is the most commonly diagnosed chronic neurological disorder in dogs, both purebred and mixed breeds, research shows that about three-fourths of epileptic dogs have idiopathic epilepsy. Many of these cases are refractory, or resistant to anticonvulsant medications, and thus, dogs with refractory idiopathic epilepsy are at greater risk of disease-related complications and death associated with their uncontrolled seizures.

"Canine epilepsy can be a devastating condition, and some dogs are resistant to standard therapies," says Dr. Diane Brown, CEO of the AKC Canine Health Foundation, which is funding research via its Epilepsy Research Initiative. "The

goal of this research initiative is to provide funds to support innovative research that will advance understanding of the mechanisms underlying epilepsy and lead to more effective treatments and educational resources for dog owners and veterinarians."

The Epilepsy Research Initiative of the AKC Canine Health Foundation is funding studies that aim to provide insights about canine epilepsy. The target areas being investigated include: identification of genetic risk factors, the work of Dr. Johnson and his team; treatment using non-psychoactive cannabidiol (CBD) oil; and the role of gastrointestinal health in epilepsy.



EPILEPSY & BLOODLINES

A 20-year veteran of studying the genetics of canine diseases, Dr. Johnson says, "We see pockets of epilepsy in certain bloodlines, and some breeders have successfully bred away from it. Granted, the process is not as effective as reducing disease would be if we had genetic markers."

Dr. Johnson believes mutations in numerous genes are likely to collectively contribute to the increased brain activity that goes beyond a normal threshold and results in epilepsy. "This could be due to changes in genes that code for ion channels, neurotransmitter receptors and a variety of other proteins that alter the seizure threshold," he explains.

"In our study, we are trying to identify DNA variants that could affect the function of genes," says Dr. Johnson. "By comparing the frequency of these variants in epileptic and non-epileptic dogs, we hope to identify genetic risk factors. Knowing what gene changes contribute to a dog's epilepsy may also help us better tailor therapies for that specific case."

Instead of the traditional method of searching for linked markers, his team is using a powerful whole-genome sequencing approach that allows them to look for DNA changes in hundreds of epilepsy candidate genes. "By using this whole-genome sequencing approach, we hope to lead the identification of the multiple DNA mutations in epileptic dogs that collectively act to affect the function of genes shown to alter the seizure threshold in humans or rodents," Dr. Johnson says.

Thus far, a few mutations have been found to be substantially more common in epileptic dogs. The next step is to validate these mutations as genuine risk factors for canine epilepsy.

"The best outcome would be a genetic test for the genes known to be associated with epilepsy, as well as a more clear understanding of how many cases of idiopathic epilepsy are indeed inherited," he says. "This would allow breeders to make more informed decisions about whether to breed a dog, as well as which matings would produce the least risk. Breeders would have another tool to use

"Knowing what gene changes contribute to a dog's epilepsy may also help us better tailor therapies for that specific case."

Gary Johnson, DVM, PhD, associate professor and molecular geneticist, University of Missouri

when evaluating pedigrees and planning future litters."

EVALUATING CBD OIL

A clinical trial to determine the efficacy of cannabidiol oil in treating dogs with drug-resistant epilepsy is underway at Colorado State University. Lead investigator Stephanie McGrath, DVM, MS, a clinician at the Veterinary Teaching Hospital Neurology Department, says, "The side effects of antiepileptic drugs are often unacceptable. There is a need for additional antiepileptic drugs that are efficacious with minimal side effects. CBD oil has been shown to have anticonvulsant properties, so controlled studies such as this one are needed to prove its effectiveness."

Dr. McGrath is studying client dogs with uncontrolled epilepsy. The goal is to enroll 60 dogs that have two or more seizures a month despite taking standard anticonvulsants. To rule out other causes of epilepsy, dogs will have a seizure evaluation, bloodwork and magnetic resonance imaging procedure.

"This is a crossover study, so dogs will receive a placebo or cannabidiol in oils given orally that look and smell the same, along with their standard antiepileptic medication, and then they will receive the opposite drug," Dr. McGrath says. "Meanwhile, owners will monitor and log their dog's seizure frequency and record medication side effects on a questionnaire."

The primary goal is to find out if cannabidiol is effective in decreasing and controlling seizure frequency in affected dogs. "It has the potential to improve the quality and length of life for dogs with uncontrolled epilepsy, while also adding a much-needed tool for veterinarians treating canine epilepsy," says Dr. McGrath.

ROLE OF THE GI TRACT

Ongoing studies at North Carolina State University College of Veterinary Medicine involve evaluating stool samples from pairs of housemate

dogs in which one is epileptic and the other is not epileptic. Epileptic dogs must be on phenobarbital alone or no anticonvulsant medications. The goal, says Karen Muñana, DVM, MS, DACVIM, professor of neurology, is to learn about the complex signaling between the GI (gastrointestinal) tract and nervous system — in other words, the microbiota-gut-brain axis.

The bacteria, viruses and fungi that live in the gut, referred to as the gut microbiota, are associated with a wide variety of health and disease conditions. A disruption of the balance of gut microbes can cause diseases, ranging from gut-associated diseases to neurological diseases.

"The mechanisms that cause refractory epilepsy, or resistance to anticonvulsant medications, are poorly understood," Dr. Muñana explains. "We believe there is an important interaction between the GI tract and the brain that is vital for maintaining homeostasis of the nervous system and that can influence a dog's susceptibility to epilepsy."

They hypothesize that dogs with idiopathic epilepsy have alterations in intestinal bacteria that result in inflammation and may impact drug-resistant refractory epilepsy. Using molecular genetic techniques, the research team will compare differences in the bacterial populations of the feces of epileptic dogs and the control dogs. They also will measure specific biomarkers of inflammation in the samples.

"We hope this study will advance the understanding of epilepsy and drug resistance and guide the development of more successful management of this disease in dogs," says Dr. Muñana. "If we find that dogs with epilepsy have different gut bacterial populations compared to dogs without epilepsy and that these bacterial populations result in gut inflammation, then that may lead to the development of alternative means to help manage epilepsy in dogs."

Meanwhile, for Lilly life is good. "Our family enjoys her so much," says Solheid. "Lilly gets two walks a day — one with me and one with my wife — going from 4 to 6 miles altogether. We take her to our lake cabin and on boat rides. She loves to be with us. We couldn't ask for more in a companion than what we have with Lilly." ■

Purina appreciates the support of the Labrador Retriever Club Inc., particularly Fran Smith, DVM, PhD, DACT, LRC vice president and health chair, in helping to identify this topic for the *Labrador Retriever Update*.

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WHAT IF...

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Helps dogs cope with external stressors like separation, unfamiliar visitors, novel sounds, or changes in routine and location

*Data was collected by Relevation Research via an online survey from August 15-19, 2018. A total of 826 nationally-representative dog owners qualified and completed the survey. Qualified participants were men and women age 18 and older, owned one or more adult dogs, were household members most responsible for taking the dog(s) to a veterinarian, and had taken the dog(s) to a veterinarian in the past 12 months.

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