PURINA PRO PLAN

POODLE Update

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EPILEPSY RESEARCH

Genetics & Innovative Treatments Are Key

POODLE EPILEPSY RESEARCH

FOCUSES ON GENE CHANGES THAT MAY INCREASE RISK

When Erika Werne adopted her 4-year-old white female Standard Poodle named "Calli" from a friend, she knew the dog had seizures and required a prescription for phenobarbital. The dog's sweet, happy disposition won her over, taking away any concerns about managing an epileptic dog.

Not a novice dog owner, Werne, of Columbia, Missouri, grew up with German Shepherd Dogs. Since then, she has owned Rough Collies, a Bouvier des Flandres and a Toy Poodle. In her job, Werne manages the eye testing database for the Orthopedic Foundation for Animals. Years earlier, she worked for the AKC (American Kennel Club) Canine Health Foundation, which funds research to learn about canine epilepsy.

"Calli had her first seizure around the time of her first heat," Werne says. "She had another around the time of her second heat, thus her owners thought it could be hormone related and had her spayed."

Spay surgery did not end Calli's seizures. In fact, they increased in severity and frequency to every two to three weeks. When Calli had a seizure, she also became incontinent and occasionally expressed her anal glands.

Werne's primary-care veterinarian consulted with specialists at the University of Missouri to individualize a treatment plan for Calli. They added a second anticonvulsant

POODLE OWNERS CAN CONTRIBUTE TO EPILEPSY RESEARCH

Owners of Poodles are encouraged to participate in epilepsy research that is part of the Epilepsy Research Initiative of the AKC Canine Health Foundation. The Poodle Club of America Foundation is among the donors to the Epilepsy Research Initiative and has awarded a separate grant to the University of Missouri study highlighted below, so the genetic analysis could be extended to Poodles. Here is how you can help:

- Contribute 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, with Standard Poodles ranking among the Top 10 of total samples received. Samples are particularly needed from Miniature and Toy Poodles. 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 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.

medication, levetiracetam, sold as Keppra®, to the phenobarbital Calli was taking.

The results were noticeable right away. "Before Keppra was added, it took Calli about 40 minutes to recover after a seizure," Werne says. "Now that she was taking both drugs, the time for full recovery was reduced by half. Plus, her seizures occurred half as often and were not as severe."

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 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,

"The best outcome would be a genetic test for the genes known to be associated with epilepsy, as well as more clear understanding of how many cases of idiopathic epilepsy are indeed inherited."

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

both purebred and mixed breeds, research shows that about three-fourths of epileptic dogs have idiopathic epilepsy, or seizures of unknown cause. 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 (see page 6). "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 goal of the Epilepsy 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."

Dr. Diane Brown, CEO,
AKC Canine Health Foundation

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.

"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 when evaluating pedigrees and planning future litters."

Meanwhile, Calli, the Standard Poodle, is doing well. Her custom treatment with phenobarbital and Keppra has helped her tremendously, Werne says. "I worry sometimes about the side effects from the medications," she says. "Phenobarbital is processed by the liver and can cause liver damage, so we go twice a year for checkups to monitor the status of her liver enzymes. I am most happy that Calli lives a relatively normal life."

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. ■

Purina thanks Pat Forsyth, vice president of the Poodle Club of America Foundation board of directors, for helping us to identify this topic for the *Poodle Update*.

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