



PURINA Pro Club

Herding Group Update

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Researchers Study MDR1 Gene Mutation in Controlling Seizures

It's 9 p.m. at Mike and Tucky Vaughan's home in rural North Carolina. Earlier that evening, Mike took the couple's three Smooth-Coated Collies, "Mac," "Kate" and "Nick," for a one and a half mile walk in a nearby park. Now, lying on the brick floor of the living room, the dogs are ready to go to bed.

Suddenly, Kate and Nick leap to their feet. Mac, the 8½-year-old Collie, has fallen off the couch and is thrashing uncontrollably on the floor. Typically in the days preceding an epileptic attack, Mac becomes clingy and fussy. This time there were no warning signs and the Vaughans are caught off guard.

Mike crates the other two dogs and rushes to help his wife, who has Mac on the floor with his head resting on the padded blue flotation cushion they bought so Mac wouldn't bang his head against the hard floor when he had a seizure.

Mac lies on his side and "paddles" vigorously, trying to get up. His teeth gnash uncontrollably at the air, and Mike is careful to sit behind him, holding his neck down with one hand while holding his body down with the other. Mike sits with Mac for almost 20 minutes before the Collie appears calm enough to sit up and take some water. The worst has passed.

While some 5 percent of dogs experience seizures, no test confirms

whether a dog actually has epilepsy. Two-thirds of dogs diagnosed with idiopathic epilepsy, meaning other possible underlying causes for the seizures have been ruled out, respond positively to medication. However, there are dogs like Mac who do not respond to conventional treatment. Despite being on full doses of the common anti-epileptic medications Phenobarbital and potassium bromide, Mac still has seizures every couple of weeks with attacks generally lasting anywhere from 30 seconds to one minute.

Resistant to Seizure Treatment

When it became evident that medicine wasn't controlling Mac's seizures, the Vaughans were referred to Karen Munana, D.V.M., associate professor of neurology at North Carolina State University College of Veterinary Medicine. Munana studies refractory epilepsy, or frequent and severe seizures despite drug therapy. Specifically, she investigates why some dogs respond poorly to medication.

Mac was found to have a mutation in the canine multi-drug resistance gene, more commonly known as MDR1. Munana and Katrina Mealey, D.V.M., Ph.D., associate professor at Washington State University College of Veterinary Medicine, are working to understand the effect of the MDR1 mutation on seizure control.

The MDR1 seizure study is funded

by grants from the Department of Clinical Services at North Carolina State University College of Veterinary Medicine and, more recently, from the Collie Health Foundation. A Seizure Studies Fund set up through the North Carolina Veterinary Medical Foundation supports ongoing studies on the diagnosis and treatment of epilepsy and dissemination of epilepsy information. For information, visit <http://cvm.ncsu.edu/epilepsyresearch/funding.html>.

Mealey identified the MDR1 mutation in 2001; she and scientists at Washington State University then developed a genetic test that helps to identify dogs that carry the mutated gene, and thus, could pass it on to their offspring. Mealey and Munana hypothesize that the MDR1 mutation may play a role in determining a dog's response to seizure medications. To test the theory, they're comparing epileptic dogs with the mutation to epileptic dogs without the mutation to see if the dogs have different responses to treatment.

The MDR1 gene encodes a transmembrane protein called P-glycoprotein that functions in a protective capacity to transport a variety of drug substrates, including ivermectin and loperamide, from the brain-barrier into the body. Dogs with a mutation in the MDR1 gene do not have this protective barrier and cannot pump some drugs out of the brain. Thus, drugs like ivermectin can cause toxic reactions that result in debilitating illness and even death.

While there is no evidence that dogs with the MDR1 mutation can't tolerate anti-epileptic drugs, Munana hopes the MDR1 study will reveal the missing links. She aims to learn why some epileptic dogs respond to seizure medications while others do not.

"Research has shown that in some cases of epilepsy, the MDR1 gene is expressed in greater than normal amounts," she explains. "This causes the P-glycoprotein pump to go into overtime, pumping seizure medications out of the brain, possibly explaining

Understanding the MDR1 Gene Mutation

Veterinarians encourage owners to test breeds susceptible to the multi-drug resistance (MDR1) gene mutation early so they will be know whether they could have a toxic reaction to certain medications. Dogs tested for the MDR1 gene mutation fall into one of three genotypes:

- **Normal/Normal:** Dogs do not carry the mutation and will not pass it on to their offspring. These dogs will not experience adverse drug reactions to normal doses of drugs known to cause toxic reactions in affected dogs.
- **Mutant/Normal:** Dogs carry the mutation and may pass the mutated gene on to their offspring. Toxicity may occur after normal doses of certain medications.
- **Mutant/Mutant:** Dogs carry the mutation and will pass the mutated gene on to their offspring. Normal doses of certain medications will cause toxicity.

Continued on page 2

MDR1 Gene Mutation

continued from page 1

why some dogs don't respond well to medication."

But for epileptic dogs with the MDR1 mutation, and particularly those with the mutant/mutant genotype (See "Understanding the MDR1 Gene Mutation" on page 1), the opposite scenario likely occurs. "Our study hypothesis is that epileptic dogs with the MDR1 mutation and a defective P-glycoprotein pump may accumulate more of the anti-epileptic drugs in their brains and have better seizure control than dogs without the mutation," Munana says.

"I have many epileptic patients with poorly controlled seizures," says Munana, explaining why the MDR1 research is important to her. "I see firsthand the financial and emotional burden that this disease places on owners and how it negatively affects a dog's quality of life."

The Vaughans understand the emotional and financial burdens only too well. Mac has had over 225 seizures. Mike Vaughan notes that Mac has become dull over time — as if his brain is encased in molasses — and he suffers from ataxia, a neurological condition causing difficulty walking. Mac's medications run close to \$100 per month, not including examinations, biannual blood tests, and gas money for trips to the veterinarian.

They remember the first few years of Mac's epilepsy as scary. "Dealing with an epileptic dog can be logistically and psychologically prohibitive at the beginning," Tucky Vaughan says. "Eventually, you come to feel competent dealing with the seizures, but watching your dog go through that will always pain you."

Since Mac has the MDR1 mutation, shouldn't he be responding to the medication? Munana points out that Mac's genotype is mutant/normal, meaning he may be more susceptible to certain drugs than dogs with a completely normal genotype, but would not be expected to be as sensitive to drugs as a dog with two mutant genes.

"The fact that Mac has one normal gene and he responds poorly to medication does in fact help support the

hypothesis of our study," Munana says. "But we need to compare his results to the results of many more animals before we can say that this finding is significant."

Seven Affected Herding Breeds

"It's hard to gauge how many veterinarians and owners are aware of the MDR1 gene mutation," says Mealey, whose laboratory recently finished a study looking at how effective P-glycoprotein is at pumping anti-seizure medications. Results of the study, funded by the Morris Animal Foundation, will be published in an upcoming issue of the *American Journal of Veterinary Research*.

Mealey's laboratory averages 200 MDR1 tests per month from the United States alone; however, she would like to see many more dogs tested, and samples of the seven herding breeds and two sight hound breeds with the MDR1 mutation submitted earlier. Collies are the most affected breed; other herding breeds are Australian Shepherds, Miniature Australian Shepherds, Old English Sheepdogs, Shetland Sheepdogs, McNab Shepherds, and English Shepherds. Affected sight hound breeds are Silken Windhounds and Longhaired Whippets. Any herding mixed breed may also have the mutation.

Washington State University is the only veterinary laboratory in the United States that runs the test for the MDR1 gene mutation. The test costs around \$60 and can be performed from a DNA cheek swab sample. MDR1 test kits may be ordered from the Veterinary Clinical Pharmacology Laboratory at Washington State University at www.vetmed.wsu.edu/vcpl/test.aspx.

Puppies may be tested for the MDR1 gene as soon as they are weaned from their mothers. "It's in a puppy's best interest to be tested," Mealey says. "We frequently receive 'rush' orders from people who need to know whether their dog has the drug sensitivity because the dog is in need of chemotherapy or similar treatment. That's why I suggest people test their dog before any potential health problems occur."

Munana and Mealey agree that

Epileptic Collie & Australian Shepherds May Contribute to Research

Collies or Australian Shepherds diagnosed with epilepsy that currently are being treated with anti-epileptic medications are being sought for seizure research at North Carolina State University. Owners interested in learning more about the study may contact Julie Nettifee-Osborne at Julie_Osborne@ncsu.edu or (919) 513-6812. Owners of dogs that qualify for the study will be sent materials to take a DNA cheek swab on their dog to be evaluated to determine their MDR1 status. There is no cost to participate.

the most exciting aspect of the MDR1 mutation and seizure study is the promise of helping to improve the everyday lives of dog and their owners. They hope to one day be able to offer more options and hope.

"As we learn more about the genetic basis of disease, we can potentially start devising methods to treat disease at a new level," Munana says. "In the past, when one anti-epileptic drug treatment failed, all we had to offer was another anti-epileptic drug. But if we learn that the MDR1 gene does play a role in seizure control, we can target therapy toward the gene or protein that is produced to try to treat resistant epilepsy."

Meanwhile, the Vaughans, who had never heard of the MDR1 gene before Mac was diagnosed, have become much more aware of the potential impact of genetics. They hope genetic testing will lead to better, more effective, treatments for dogs like Mac.

"Mac is a wonderful example showing that it pays to hang in there," Mike Vaughan says. "I'm sure we're better people because of him, and we owe him that." ■

Want to Reach the Editor?

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Drugs to Avoid in Dogs with the MDR1 Gene Mutation

Many types of drugs have been reported to cause problems in Collies and other herding dogs affected by the MDR1 gene mutation. The list of drugs causing a reaction is likely to grow as research continues.

Drugs that have been documented to cause problems include:

- Ivermectin (anti-parasitic agent);
- Loperamide (over-the-counter anti-diarrheal agent contained in Imodium®);
- Doxorubicin, vincristine, vinblastine (anti-cancer agents); and
- Digoxin (heart drug).

For a complete list of drugs reported to cause problems in dogs that carry the MDR1 mutation, visit <http://www.vetmed.wsu.edu/depts-VCPL/drugs.aspx>.

Source: Katrina Mealey, D.V.M., Ph.D., associate professor at Washington State University College of Veterinary Medicine.