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***POODLE* Update**

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RESEARCH OF ADDISON'S DISEASE IN STANDARD POODLES

FOCUSES ON GENETIC DIVERSITY &
FINDING THE MUTATION



Shimmer Ring Standard Poodle breeder Valerie Wilmot of Euless, Texas, believes in breeding dogs that are beautiful and healthy. Her dedication to the breed spans more than 25 years so when she introduced a sire to her breeding program a few years ago that was later diagnosed with Addison's disease, she was crushed.

"I had never had a dog with Addison's disease," Wilmot says. "This was an incredible disappointment, plus it was a loss to me and my breeding program. It also was a loss to the breed, as he is a very nice dog."

Dogs are often middle age when Addison's disease is diagnosed. Thus, they may already have been

bred and played a role in proliferating the incidence rate.

The 2-year-old male dog was a stunning show champion that had passed the breed's health tests. Wilmot had great expectations for breeding him again, but those fell apart shortly after the first litter was born and the sire was diagnosed with Addison's disease.

Lethargy and loss of appetite were the first signs Wilmot noticed indicating that something could be wrong with the male Standard Poodle. "I told the veterinarian he just wasn't himself," she says.

"WITH ADDISON'S DISEASE, RESPONSIBLE BREEDERS CAN INADVERTENTLY CONTRIBUTE TO PRODUCING AFFECTED DOGS AND CARRIERS."

Shimmer Ring Standard Poodle breeder Valerie Wilmot

A blood test showed the dog's electrolytes were not normal. Suspecting Addison's disease, the veterinarian ran an ACTH (adrenocorticotropic hormone) stimulation test to check the dog's level of cortisol, a hormone that helps the body adapt physiologically to stress. During an ACTH test, a normal dog responds with an elevation in its cortisol level, but a dog with Addison's disease is not able to output enough cortisol for a normal response. The test confirmed the disease in Wilmot's dog.

Fortunately, the Standard Poodle responded well to treatment with medications. Understanding the risk of breeding an affected male, Wilmot had the handsome male neutered. Like many other breeders, she was frustrated that she had bred

the dog without knowing he had Addison's disease. Her good intentions to breed a healthy litter backfired due to no fault on her part.

"With Addison's disease, responsible breeders can inadvertently contribute to producing affected dogs and carriers," Wilmot says.

'THE GREAT PRETENDER'

Also known as primary hypoadrenocorticism, Addison's disease is an immune-mediated disease in which the body attacks the outer layer of adrenal glands, or small organs near the kidneys, causing a deficiency in the essential steroid hormones cortisol and aldosterone. Cortisol, a glucocorticoid, helps the body deal with stress via an inflammatory response linked to the immune system. Aldosterone, a mineralocorticoid, helps regulate water and electrolyte levels by maintaining the body's balance of sodium and potassium.

Addison's disease is sometimes called "The Great Pretender" because it mimics conditions such as inflammatory bowel disease, liver disease and acute kidney failure. The disease destroys the adrenal cortex, or outer layer of adrenal glands, and subsequently the body's ability to produce these key hormones. Fortunately, therapy to replace the hormones the body can no longer produce usually results in successful disease management.

"Addison's disease is very treatable," says Steven G. Friedenberg, DVM, PhD, DACVECC, assistant professor in the Department of Veterinary Clinical Sciences at the University of Minnesota. "Because dogs will require lifelong medications and monitoring, it's important to develop a good relationship with a veterinarian you trust who is comfortable treating the disease."

Treatment typically consists of monthly injections, either Percorten®-V or Zycortal®, given by the veterinarian to replace the mineralocorticoid, aldosterone, plus daily doses of prednisone to replace the steroid cortisol. Some owners opt to give

STANDARD POODLE OWNERS CAN HELP ADVANCE RESEARCH OF ADDISON'S DISEASE

Researchers at the University of Minnesota College of Veterinary Medicine are seeking blood samples from Standard Poodles for their study of Addison's disease. The goal is to identify a gene mutation so that a genetic test can be developed to help reduce disease incidence.

To participate in the study, which is funded in part by the Poodle Club of America Foundation, Standard Poodles of any age with Addison's disease are eligible, as well as Standards over age 10 that do not have Addison's. Shipment of blood samples for eligible dogs is covered by the study.

To learn more about this study, please contact [Dr. Steven Friedenberg](#) or visit the University of Minnesota College of Veterinary Medicine [website](#).



their dogs a daily pill, Florinef,[®] rather than the monthly injections. The best treatment for an individual dog can vary. For example, dogs with atypical Addison's disease, in which only part of the adrenal cortex is affected, may do well with prednisone and not need the additional medications.

The disease is not unique to Standard Poodles. [Other breeds having a high heritability](#) are Bearded Collie, Nova Scotia Duck Tolling Retriever, and Portuguese Water Dog. As with dogs, people develop Addison's disease when their adrenal glands are damaged, thus triggering insufficient amounts of cortisol and aldosterone.

Due to the prevalence of the condition in Standard Poodles, the Poodle Club of America Foundation (PCAF) is supporting two grants aimed at learning more about Addison's disease. Both are in the second phase of earlier research that also was supported by PCAF.

A study underway at the University of California-Davis is investigating genetic diversity in Standard Poodles and its impact on autoimmune diseases such as Addison's disease. Meanwhile, at the University of Minnesota, researchers aim to better understand what triggers Addison's disease in Standard Poodles, with a goal of identifying the gene mutation and developing a genetic test to identify affected dogs and carriers to aid breeding programs.

A COMPLEX INHERITANCE

Wilmot is excited to have contributed a DNA sample of blood from her affected dog to the University of Minnesota study. Lead investigator Dr. Friedenberg encourages owners of affected dogs and those with normal dogs over age 10 that qualify for the study to participate. (See page 3 for more information about participating.)

"Addison's is a complex inherited disease," says Dr. Friedenberg. "It is highly likely to involve both genetic and environmental factors. For now, we are focusing on genetics. We want

to better understand the genetic variants or mutations that trigger the disease as we work to develop a genetic test to help decrease the disease incidence."

An earlier study led by Dr. Friedenberg was the first published genome-wide association study looking for polymorphisms associated with Addison's disease in Standard Poodles. The research, published in *Mammalian Genome* in February 2017, involved phenotyping 133 Standard Poodles, including 61 affected dogs and 72 unaffected ones. No genetic markers were found, so next they sequenced the entire genomes of 20 Standard

SIGNS OF ADDISON'S DISEASE

- Lethargy
 - Vomiting
 - Diarrhea
 - Finicky appetite
 - State of shock
-

Poodles, a group consisting of 13 affected dogs and seven unaffected ones, to identify common variants across affected dogs and variants segregating within a single pedigree of highly affected dogs.

"We hypothesized that a combination of a genome-wide association study and whole-genome sequencing study would allow us to identify specific causative variants that lead to the development of Addison's in Standard Poodles," explains Dr. Friedenberg. "However, we were unable to pinpoint any specific causative variants based on our current understanding of the way genes function."

Going into the study, the researchers believed that Addison's disease in Standard Poodles was due to an autosomal recessive inheritance pattern, meaning both the sire and dam must carry the gene mutation to produce an affected dog.

"Because we could not identify a genetic marker, this suggests

that Addison's disease may have a complex inheritance pattern or be relatively fixed within Standard Poodles, or there could be some combination of the two," Dr. Friedenberg says. "However, we identified several candidate genes that may be fixed in Standards and in a small population of related breeds, which could contribute to the disease."

Citing a study published in May 2015 in *Canine Genetics and Epidemiology*, Dr. Friedenberg says the effects of genetic bottlenecks are believed to have contributed to high inbreeding in Standards and the development of Addison's disease. "This work is consistent with our findings," he says. "Based on this group's analysis of relatedness and heterozygosity among inbred dogs, they concluded that some of the genes responsible for Addison's may be fixed within the breed. This would support our inability to detect a single causative marker in our study of 133 dogs."

As Dr. Friedenberg and his team continue to study the genetic causes of the disease in Standard Poodles, they are planning to genotype a larger population of dogs. "We also may use a cross-breed approach to help identify disease-associated markers or causative polymorphisms," he says. "There is much to learn about the genetics of this disease."

GENETIC DIVERSITY ROLE

Research of genetic diversity — including the 2015 study cited by Dr. Friedenberg — and how it contributes to Addison's disease is ongoing. Niels C. Pedersen, DVM, PhD, distinguished professor emeritus at the University of California-Davis School of Veterinary Medicine, leads the effort to understand how genetic bottlenecks and inbreeding have contributed to the incidence of the autoimmune diseases sebaceous adenitis and Addison's disease in Standard Poodles.

"Our hypothesis is that these diseases increased rapidly around the mid-20th century," Dr. Pedersen says. "We believe extensive inbreed-

ing started with a small group of founders that produced widely used show-winning offspring. This artificial midcentury bottleneck created a severe breed-wide genetic imbalance with two-thirds of the most popular inbred dogs possessing only one-third of available breed-wide genetic diversity. This has prompted breeders to make a conscientious effort to select parents that will produce the most genetically diverse puppies.”

Sebaceous adenitis, an inherited skin disease in which the sebaceous glands become inflamed and can cause hair loss, and Addison’s disease are believed to have cropped up in the breed due to the extensive inbreeding at that time. Meanwhile, genetic outliers remained relatively disease-free. As breeders selected for the desired phenotypic traits of the Standard Poodles, this led to intense inbreeding and the inadvertent amplification of these disease-associated traits.

The search to learn how much diversity still exists in the breed was the crux of the work published in 2015 in *Canine Genetics and Epidemiology*. The study included 761 dogs — Standard Poodles, Miniature Poodles and Miniature/Standard crosses — from the U.S., Canada, and Europe. Miniature Poodles, which are considered genetically distinct and relatively free of these diseases, are sometimes used as outcrosses to try and eliminate the disease traits.

“We determined that most of the Standards in the world are genetically similar, with essentially 70 percent of the genetic diversity in the breed existing in just 30 percent of dogs,” explains Dr. Pederson. “They have a great deal of genetic diversity compared to other breeds of dog, but this genetic diversity is imbalanced.”

The goal is to learn how genetic diversity relates to health and to create an opportunity for breeders who want to maximize diversity to breed healthy dogs. Potentially,

breeders may be able to compare genetic profiles of possible mates to find out whether a low coefficient of inbreeding reflects relatedness of the two dogs.

Dr. Pederson is optimistic that it may be possible to redistribute the genetic diversity in Standard Poodles by carefully choosing breeding partners based on genetic testing over a number of generations. “This undertaking should reduce the incidence of deleterious simple recessive traits as well as complex genetic disorders such as these autoimmune diseases,” he says. “The emphasis of mate selection should be on maximizing genetic differences by augmenting information from pedigrees and genetic tests that accurately measure diversity across the genome.”

Reflecting on her litter sired by her male with Addison’s disease, Wilmot says, “This disease can happen to anyone. The more I’ve talked to other breeders, the more I’ve realized this. I don’t believe we should just shrug our shoulders. I feel like part of being a responsible breeder is trying to find answers to these problems by supporting the research.”

“Fortunately, most dogs go on to lead full, healthy lives,” Dr. Friedenberg says. “It seems the signs of Addison’s disease often are associated with stress. If owners notice a link between stress and these signs, they should talk to their veterinarian.”

Considering the prevalence of the disease, Dr. Pederson says, “The risk factors for Addison’s disease appear fixed in all Standard Poodles. Some breedings will produce a little higher risk and some a little lower risk, but no breeding will guarantee puppies without a risk of developing Addison’s.” ■

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*.

Want to Reach the Editor?

Have comments about the *Poodle Update*? Send them to [Barbara Fawver](#), Editor, Nestlé Purina PetCare.

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