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Research Focuses on Understanding the Genetics Behind Addison's Disease

When her Bearded Collie, "Maggie" (Alashaw's Up and At Em,' OA, OAJ, NAC, OJC, CGC) collapsed, Jenny Scheytt of Sterling Heights, Mich., knew something was wrong, so she took the dog to an emergency veterinary clinic. Though the emergency veterinarian who treated Maggie had not seen many cases of Addison's disease, he recognized the possibility partly because Bearded Collies are among the affected breeds.

The veterinarian performed an adrenocorticotropic hormone (ACTH) stimulation test on Maggie, which confirmed the diagnosis. The stimulation test, the only definitive diagnostic tool for Addison's disease, is used to determine whether the adrenal gland produces the corticosteroid hormone cortisol, which is important in regulating metabolism, stress, reproduction and immune system function.

"Prior to Maggie's collapse episode, the only sign that she had Addison's was an occasional lack of appetite," says Scheytt, who breeds Bearded Collies under the Estrella prefix. "In fact, just the weekend before, she had competed in an agility trial. Maggie had never eaten well, especially as a puppy, so I didn't think a lot about it. When she was about 18 months old, I took her to the veterinarian because I was concerned that she was getting thin. A complete blood count analysis did not detect an abnormality."

Reflecting on the events leading up to the diagnosis, Scheytt says, "We were at the agility trial on a Sunday and by Thursday the next week, Maggie started acting weird and not eating. By Friday, she wasn't eating anything and was listless. Within 24 hours, she had totally crashed."

Hypoadrenocorticism, or adrenal insufficiency, is more commonly known as Addison's disease. Named for the British physician Thomas Addison, who described the condition in humans in 1849, Addison's disease is a genetic condition that mimics other illnesses. Signs may occur suddenly and severely or may wax and wane. As a result, dogs with Addison's disease sometimes are mistaken for having conditions such as inflammatory bowel disease, hepatic or liver disease, or acute kidney failure.

Addison's disease first was recognized in dogs in 1953. Although the disorder can occur in any breed, those considered susceptible are Bearded Collies, Great Danes, Leonbergers, Nova Scotia Duck Tolling Retrievers, Portuguese Water Dogs, Standard Poodles, and West Highland White Terriers. Fortunately, dogs can live normal lives when they are monitored and treated with medications.

Malfunctioning adrenal glands are the source of the problem. Located on top of the kidneys, the adrenal glands secrete hormones into the bloodstream. The adrenals have two layers. The outer area, the cortex, produces corticosteroid hormones, such as cortisol, which impacts metabolism and helps the body deal with stress, and aldosterone, which is important in regulating electrolytes. The inner area, the adrenal medulla, is part of the sympathetic nervous system. It produces epinephrine, or adrenaline, and usually is not affected by Addison's disease.

Three types of Addison's disease are recognized: primary, atypical and secondary. The two former types are most likely caused by immune-related damage to the adrenal glands. The secondary type is caused by tumors, long-term steroid use or failure of the pituitary gland to simulate the adrenals with adrenocorticotropic hormone. Identifying the type of Addison's disease through an ACTH stimulation test is important in order to provide proper treatment.

The ACTH stimulation test evaluates a dog's response to the pituitary hormone ACTH. A blood sample is taken, and a dog's resting cortisol level is measured. Then, the dog is injected with a form of ACTH, which tells the adrenals to produce cortisol. After an hour, the blood is drawn again to measure the stimulated cortisol level. A dog that does not respond to the ACTH stimulation with an increase in cortisol hormone level is diagnosed with Addison's disease.

"Most dogs are diagnosed with primary Addison's disease, which means there is a slow degradation of the adrenal cortex over time," says Anita Oberbauer, Ph.D., professor and chairwoman of the Department of Animal Science at the University of California-Davis. "Eventually, there is nothing left of the organ to produce cortisol and aldosterone. The dog's mineral balance and metabolism are disrupted, and that's why the signs are so diffuse."

Addison's disease typically develops in middle-aged dogs between 4 and 6 years old but can appear in dogs as young as 15 weeks or as old as 12. Males and females are equally affected. Maggie, who was 4 ½ years old, fit the profile.

The veterinarian prescribed a replacement hormone therapy for Maggie that was effective in treating her Addison's disease. "It took about one month before Maggie was her old self again," Scheytt says. "Soon, she was back to doing agility and herding."

Several medications are used to

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How to Contribute to Genetics Research

Breeders and owners of healthy dogs and those affected by Addison's disease may contribute to research to discover the gene mutation at the University of California-Davis. Anita Oberbauer, Ph.D., professor and chairwoman of the Department of Animal Science, leads the research.

Blood samples are requested for affected dogs and unaffected dogs over the age of 7 from these breeds: Bearded Collies, Great Danes, Portuguese Water Dogs, Standard Poodles and West Highland White Terriers. There is no cost to participate, although owners are responsible for having a veterinarian collect the blood sample and shipping the sample to the research laboratory. To request a sample kit, visit *www.cgap.ucdavis.edu*. You also may send an e-mail to Dr. Oberbauer at amoberbauer@ucdavis.edu.

Addison's Disease

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treat Addison's disease. Initially, a mineralocorticoid replaces the aldosterone, the hormone responsible for maintaining electrolyte levels. The mineralocorticoid is replaced with an oral medication, fludrocortisone acetate, or an injectable medication, desoxycorticosterone pivalate. The cortisol normally secreted by the adrenals is replaced with oral prednisone. Monthly costs for medications vary but average around $65.

A Type of Autoimmune Disease

Primary and atypical Addison's disease are autoimmune diseases in which the body creates antibodies to its own adrenal tissues, targeting the cortex for removal by the immune system. The generation of the self-directed antibodies is due to a genetic susceptibility that is likely triggered by unidentified factors, such as the environment or medications.

Hypothyroidism is the most frequently reported autoimmune disease in dogs. Signs include thick, oily skin, obesity and lethargy. Other autoimmune diseases can affect functioning of the endocrine glands, bowels, joints, kidneys, heart, lungs, blood and the nervous system.

Symmetrical lupoid onychodystrophy (SLO) is an autoimmune disease that causes dogs to lose claws. Eventually all claws may be lost. Signs include receding quicks, split claws, secondary infection, pain and lameness. Similar to Addison's disease, treatment controls SLO.

Ginny Aulik of Rockford, Ill., describes when her Bearded Collie "Willow" was diagnosed with the condition. "A visit to the veterinarian resulted in a diagnosis of SLO," she says. "Supplements of an omega fatty acid and a pentoxifylline medication known as Trental, which helps to improve blood flow, resolved her lameness and loss of claws."

Aulik's experience with another autoimmune disease in 2002 with her Bearded Collie, CH Desertstorm Secret Formula, who won Best of Breed at Westminster that year, was not as simple. "'Felix' did not have any signs of disease other than toward the end when his topline fell due to pain from kidney disease," she says. "He died in December that year from immune-mediated renal failure. He was diagnosed in June after a wellness checkup indicated high BUN (blood urea nitrogen), creatinine and protein in the urine. He had no other signs of being ill. He romped around just like normal."

Signs of Addison's disease can be ambiguous. "A dog with Addison's disease may seem lethargic, listless or depressed," says Oberbauer. "Owners sometimes say their dog seemed 'off' or 'lost the sparkle in his or her eye.' Lack of appetite is a good indicator, but other signs include vomiting, diarrhea and muscle pain."

Owners may notice a dog having pain in the hind quarters or not being able to jump onto a bed or couch as in the past. Shivering or muscle tremors also are signs. If the adrenals continue to deteriorate, a dog may have an acute episode or Addisonian crisis. Potassium levels are elevated, and the heart rate slows and may even stop. Arrhythmia can result, and blood pressure may drop dangerously low.

It often takes a serious incident, such as Maggie's collapse episode, before a diagnosis is made. Researchers indicate a dog with Addison's disease may have depleted 85 to 90 percent of its adrenal hormone reserves before showing clinical signs. Stress from injuries, exhaustion or severe environmental conditions may trigger the condition.

Making Genetics Progress

Research of the genetics of Addison's disease indicates that the disease is regulated by a major gene inherited in a recessive mode of inheritance, though not necessarily in a simple autosomal recessive inheritance pattern as other factors seem to govern onset of the disease. "This means for Addison's to be passed on, it appears that both the sire and dam have to carry a recessive gene for this disease," says Oberbauer who has studied Addison's disease in dogs since 2001.

Linda Aronson, D.V.M., health chairwoman of the Bearded Collie Club of America and vice president of the Bearded Collie Health Foundation, says, "Presentations at this year's Tufts University genetics conference indicate that 30 to 40 genes may be involved in each autoimmune disease. While some are common to all autoimmune diseases, others are disease-specific. Some genes are protective, and others increase risk.

"Layered on these are the triggers that make a particular animal ill. These can be environmental, or medications, but most are unknown. Other factors, such as penetration, expression and epigenetics, also are involved in whether a dog will get sick. For example, there is a litter of Beardies in the U.K. in which both parents developed Addison's after the puppies were born. All the puppies would be genetically programmed for Addison's if the disease were simple autosomal recessive, yet they are 11 years old now and none has developed Addison's."

Oberbauer's research focuses on identifying the causative gene mutation in Bearded Collies, Great Danes, Leonbergers, Standard Poodles, Portuguese Water Dogs, and West Highland White Terriers. The AKC Canine Health Foundation has funded the research with support from the Bearded Collie Club of America, Bearded Collie Health Foundation, Poodle Club of America, Leonberger Club of America, Portuguese Water Dog Foundation, and Great Dane Club of America.

"My first Bearded Collie was diagnosed with Addison's in 1989 when there was little information about this disease," says Aronson. "It was a labor of love to find information. By supporting the genetic research, we hope to help advance understanding."

Oberbauer's collaborative research effort involves Äke Hedhammar, professor of small animal medicine at the Swedish University of Agricultural Sciences, and Kerstin Lindblad-Toh, Ph.D., director of Vertebrate Genome Biology at the Broad Institute and professor at Uppsala University. The team is analyzing DNA from Addisonian dogs from around the world to identify the genetic changes responsible for Addison's disease.

Oberbauer and her team have collected and analyzed DNA samples from 1,700 Bearded Collies. The findings indicate that 7 percent of the sample was affected by Addison's disease, slightly higher than the 2 to 4.6 percent reported in a health survey conducted by the Bearded Collie Club of America.

DNA samples they have collected from other breeds also show higher than expected population prevalence, which Oberbauer attributes to interested owners or those with affected dogs submitting samples more frequently than the general public. The prevalence rates for Great Danes, Leonbergers, Portuguese Water Dogs, Standard Poodles and West Highland White Terriers are 8.9 percent, 3.2 percent, 5.9 percent, 15 percent and 17 percent, respectively.

As the research has evolved, Oberbauer has looked for commonalities among autoimmune disorders. "There may be some common genetic regions that confer a greater susceptibility to some of these disorders that may be autoimmune," she says. "Studies of hypothyroidism and Addison's in the Bearded Collie both point to an autoimmune region on chromosome 4. I am optimistic that we will find a marker and possible gene mutation that increase the risk of these diseases."

Discovery of the gene mutation for Addison's disease would help breeders in making breeding decisions. For now, Oberbauer cautiously advises breeders to not disregard dogs with valuable characteristics. "I encourage breeders not to eliminate a potential carrier of Addison's disease, or another autoimmune disorder, if the dog has phenomenal attributes," she says. "You could easily trade one disorder for another. Any breeding decisions regarding potential carriers must be made by prudently selecting a complementary mate that has very little likelihood of being a potential carrier to minimize affected offspring."

Meanwhile, owners of dogs with Addison's disease cope by monitoring and treating them. Maggie, who is 10 ½ years old, no longer competes in agility, but she is a healthy, active dog. "If treated with proper medications, these dogs go on to lead normal lives," Scheytt says. "Stress can affect Maggie, but I have learned to recognize signs. She should never have another crash." ■