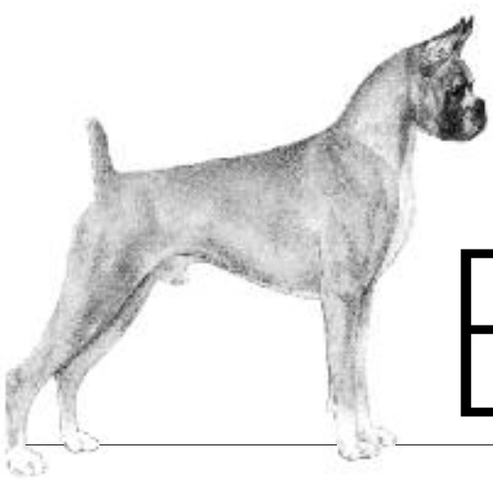

PURINA Pro Club®

Boxer Update

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ARVC Gene Mutation Discovery Gives Breeders Another Testing Tool

When a breakthrough in the discovery of the gene mutation that causes arrhythmogenic right ventricular cardiomyopathy (ARVC) in Boxers was announced in April 2009, breeders were ecstatic. Finally, Boxers could be tested for the heart disease that oftentimes causes sudden death with no warning signs.

The lead investigator, Kathyrn M. Meurs, D.V.M., Ph.D., the Richard L. Ott Professor of Small Animal Medicine and Research and director of the Veterinary Cardiac Genetics Laboratory at Washington State University College of Veterinary Medicine, had studied the genetics behind the fatal heart disease for more than 12 years. Collaboration with Kerstin Lindblad-Toh, Ph.D., co-director of Genome Sequencing and Analysis at the Broad Institute of MIT and Harvard, helped localize the disease to a specific region on a chromosome.

"We narrowed down candidate genes until we found a genetic deletion in a gene that produces striatin, a key binding protein that helps hold together cardiac cells," Meurs explains. "The finding is similar to what is known about the disease in humans. In fact, much of what we know about this disease in humans is applicable in dogs."

Though the discovery brought promising news, ARVC continues to be a confusing disease. In humans, there are 141 different mutations located in eight different genes that individually can lead to development of the disease. This may be the case in the Boxer as well. Additionally, as in people, other factors may affect the severity of the disease. Environmental factors, such as diet, exercise and viruses, or other genetic influences may impact the disease.

For example, Meurs found that a small number of Boxers without the gene deletion had Holter monitor test results suggestive of ARVC. She says these results could indicate other health problems, especially in Boxers under 3 years of age. Inflammation of the heart muscle due to viruses, such as parvovirus, parasites or tumors could be the culprit.

Holter monitor testing, performed over 24 hours, is considered the best method for evaluating a Boxer for cardiomyopathy. The test detects ventricular premature complexes (VPCs), which occur when the heart's lower right ventricle contracts earlier than it should, resulting in a heartbeat without a corresponding pulse. A Boxer with occasional VPCs may not show signs of ARVC, but one with multiple, successive VPCs is not able to produce a normal, effective contraction. This results in a decreased flow of blood to the brain and other vital organs. A prolonged run of VPCs can lead to cardiac arrest and death.

The striatin-deletion mutation may not be the only mutation that causes ARVC in the Boxer. In samples of ARVC-affected Boxers from the United Kingdom, only 71 percent had the deletion mutation; 29 percent did not. The findings show that the DNA test may not predict ARVC in all Boxer populations.

"We believe in Boxers that ARVC has an autosomal dominant mode of inheritance with variable penetrance," Meurs says. "Some individuals with the mutation never develop the disease. In human beings, only about 50 percent of individuals with one of the known genetic mutations actually show the disease. Therefore, although some dogs will have a severe form of the disease and die, some will have a mild, manageable form, and some will never show evidence of the disease.

"Boxers may inherit one copy of the mutated gene, making them heterozygous positive, or two copies, making them homozygous positive. Boxers that are homozygous positive for ARVC seem to have a more severe form of the disease. Though this does not mean these dogs develop ARVC sooner, it does mean that when they develop VPCs, they may have more of them.

"It is highly likely there is more than one mutation in the Boxer dog that may lead to this disease in some bloodlines," Meurs continues. "Not all dogs with VPCs have ARVC, and not all dogs with the mutation will show clinical signs of ARVC. While our test is a valuable tool, it is clearly not predictive in all Boxer populations."

Lindblad-Toh agrees. In a letter published in the January 2010 issue of the *ABCF Messenger*, Lindblad-Toh wrote: "We believe we have found a gene involved in the disease, but that several genes contribute. These may or may not be the same in U.S. and European dogs. Dr. Meurs and

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Breeding Recommendations for Boxers with ARVC

Determining whether to breed a Boxer with quality attributes that has been diagnosed with arrhythmogenic right ventricular cardiomyopathy (ARVC) can be challenging. Longtime ARVC researcher Kathryn M. Meurs, D.V.M., Ph.D., of Washington State University College of Veterinary Medicine, advises to avoid overzealous culling of dogs that could reduce genetic diversity. She suggests:

- Boxers that are heterozygous positive, or have one copy of the mutated gene and one normal gene, should be carefully evaluated for signs of disease using Holter monitor testing and possibly an echocardiogram. Dogs that do not show signs of ARVC and have positive attributes could be bred to dogs that are negative for the mutation. Puppies should be screened over a few generations, and those that are negative for ARVC may be selected to replace the mutation-positive parent and gradually decrease the number of mutation-positive dogs from the population.
- Boxers that are homozygous positive, or have two copies of the mutated gene, should not be bred unless they are an exceptional quality and it is important to maintain their positive attributes. These dogs have more severe disease and will certainly pass the mutation on to their offspring. They should only be bred to a negative dog. After two generations of negative crosses, a negative puppy could be selected as a replacement.

ARVC Gene Mutation

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researchers at Broad are continuing this work to find other genes. Once the whole picture is understood, testing for all involved genes will be possible. We therefore would like you to understand that the current testing is not comprehensive but that we are working hard to make it better."

An Adult-Onset Heart Disease

ARVC was first documented in Boxers in the early 1970s when sudden death began occurring even in young, healthy adult dogs. Some had fainting episodes during the months preceding their sudden death, while others had no signs anything was amiss.

As this was before the Internet and health registries, Boxer breeders had only rumors to go on. Among the dogs that "just dropped dead" were some of the breed's most influential producers.

The sudden deaths were truly sudden. A Boxer would be frisking around one second and fall over the next, dying within minutes. Owners seldom thought about getting an autopsy.

"Even when autopsies were done, they often did not include the specialized procedures that would yield a diagnosis," says Theresa Garton, M.D., a longtime Boxer breeder and member of the American Boxer Club Health and Research Committee.

By the early 1980s, the condition was named Boxer cardiomyopathy and believed to be hereditary. Little could be done to avoid the disease, especially since Boxers often had already been bred when signs developed.

In 1995, the American Boxer Charitable Foundation (ABCF) conducted a breed health survey that indicated heart disease was the top health concern of Boxer breeders. In 1997, while at The Ohio State University College of Veterinary Medicine, Meurs began working to identify the gene mutation. The research was supported by ABCF and the Canine Health Foundation.

DNA samples were collected from three large families of Boxers with ventricular arrhythmia. Meurs performed molecular genetic evaluations of the samples and determined that Boxers inherit the condition as an autosomal dominant trait. Males and females are affected equally, and the disease occurs in nearly every generation, although two affected parents can produce an unaffected dog.

Meurs also evaluated Boxers that experience ventricular arrhythmia but do not show signs of heart disease. She followed the progress of 150 Boxers more than 4 ½ years old that experienced more than 50 VPCs during Holter monitor testing. Dogs were evaluated annually through an owner questionnaire, physical examination, Holter moniter test, electrocardiogram and echocardiogram. She aimed to learn if there was a statistical relationship between the likelihood of collapse or heart failure related to diet, VPC occurrence, heart rate and exercise.

In 2005, Meurs moved to Washington State University to continue the research. She renamed the fatal heart disease arrhythmogenic right ventricular cardiomyopathy to more precisely describe the condition.

A disease of the heart muscle, ARVC occurs in dogs that experience erratic heartbeats, or arrhythmia, due to the early contraction of the lower right ventricle. This results in disturbed electrical impulses that not only direct the heart to beat in the first place, but also enable the heart to maintain a steady, regular rhythm.

Testing for the ARVC Mutation

For information about testing for the genetic mutation associated with development of ARVC in Boxers, go to the Web site of the Veterinary Cardiac Genetics Laboratory at Washington State University: *www.vetmed.wsu.edu/deptsVCGL/Boxer/index.aspx*.

The genetics of ARVC and the human heart disease arrhythmogenic right ventricular dysplasia (ARVD) are believed to be similar. ARVD is also considered a disease of variable penetrance in which some individuals with the mutation do not show signs of the disease until they are older, and others never show signs. In identical twins with the mutation, one twin may develop severe heart disease, while the other does not. Researchers believe that certain environmental or genetic factors may trigger the severe form of the disease.

Creating a 'Holter Monitor Culture'

A longtime advocate of Holter monitor testing, Meurs recommends that breeders begin testing Boxers at 3 years of age. She also advises to repeat the testing annually due to the fact that ARVC occurs in dogs at widely varying ages. "A single Holter reading that is normal at one point in a Boxer's life does not mean that the dog will never have ARVC," she says. "It simply means that the dog does not have the disease at that time."

The increasing number of Boxer breeders who regularly Holter monitor test their breeding stock has helped to improve the heart health of the breed. Responsible breeders preface every stud inquiry with their bitch's most recent Holter report and a request for a copy of the stud dog's annual report. Some Boxer breeders attribute Meurs with having virtually single-handedly created a "Holter monitor culture" in North America that has helped to greatly reduce the incidence of early death in Boxers.

The goal in managing ARVC is to diagnose the disease before signs develop. Beta blockers and antiarrhythmic medications are prescribed by a veterinarian or veterinary cardiologist to help prevent severe arrhythmia or congestive heart failure.

When the lower right ventricle fails to contract properly, pressure rises in the left atrium, causing fluid accumulation. Dogs with fluid in the lungs, or pulmonary edema, resulting from congestive heart failure, often develop a cough, shortness of breath and lethargy. More ventricular arrhythmias may also occur. By the time these signs appear, the disease is well-progressed.

Holter monitor testing is effective in detecting VPCs in Boxers since the arrhythmia is intermittent and may not occur during a standard three-minute electrocardiogram (ECG) test. Likewise, an echocardiogram, or an ultrasound of the heart, is not effective in detecting VPCs unless they occur frequently.

Essentially a portable ECG, the Holter monitor provides information about heart rhythm over a 24-hour period. The longer testing period usually is sufficient to detect both single VPCs and VPC runs. An abnormal Holter monitor test can help predict dogs that may later experience sudden death or develop cardiomyopathy and congestive heart failure.

Though the striatin-deletion genetic mutation is not an absolute test for ARVC, it can be used to guide breeding decisions. "Breeders should not make drastic decisions," Meurs says. "Each dog and each family bloodline should be considered individually. Removal of a significant number of dogs from the breeding population could be bad for the Boxer breed. Breeders should remember that dogs that carry this mutation also carry other important good genes that we do not want to lose from the breed."

"Nothing about this disease has ever been black and white, save the sudden cardiac death associated with it," Garton says. "Dogs with 'affected' Holter test results may live long lives without any noticeable heart problems, while other dogs with 'normal' results may experience sudden death. I think the striatin-deletion mutation test has validity and that it will be useful for us if used responsibly, but there is still much we do not know." ■

Reference: Meurs KM, Mauceli E, Acland G, Lindblad-Toh K. Genome-Wide Association Identifies a Mutation for Arrhythmogenic Right Ventricular Cardiomyopathy in the Boxer Dog. *J Vet Int Med.* 2009;23(3):687-688.

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