Boxer DNA Tests Aid Understanding of Heart & Neurologic Diseases

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Boxer breeders are fortunate to have genetic tests for the well-known heart disease arrhythmogenic right ventricular cardiomyopathy (ARVC) and the progressive disorder degenerative myelopathy (DM).

Both diseases are believed to involve multiple genetic and environmental factors besides the causative gene variant for which their DNA tests screen. Nonetheless they are helpful tools. The American Boxer Club includes both genetic tests in its recommendations for Health Screening for Boxers in a Breeding Program.

ARVC has an autosomal dominant mode of inheritance, meaning affected dogs need only one copy of the deletion mutation in a gene producing striatin, a key binding protein involved with the heart's electrical functioning. The heart muscle disease has variable penetrance in which some Boxers die suddenly following a run of ventricular premature complexes (VPCs) or succumb over time from congestive heart disease, yet other dogs develop a mild, medically manageable case.

Likewise, DM is a complex genetic disease. Although it is an autosomal recessive disorder in which an affected Boxer inherits the superoxide dismutase 1 gene (*SOD1*) mutation from both its sire and dam, the neurodegenerative disease has incomplete penetrance. Thus, only some affected at-risk dogs develop the disease, though all Boxers with the mutation pass the mutant alleles to their offspring.

As both diseases develop in adult dogs — ARVC occurs on average at 6 years of age and DM at 9 years of age — it is possible that a Boxer has already been bred when a gene mutation is recognized. If dogs are not genetically tested early in life, clinical signs of heart disease or the neurodegenerative disorder may trigger the discovery.

ARVC Mutation & Variable Penetrance

Sadly, arrhythmogenic right ventricular cardiomyopathy is found in Boxers across the U.S. In studies at North Carolina State University, where the ARVC gene mutation was discovered, of nearly 2,000 Boxers tested, 41 percent had one copy of the gene mutation, 6 percent had two copies, and 53 percent were negative.

"Removing nearly half of the Boxers from the breeding population would have a devastating effect on the gene pool," says Kathryn M. Meurs, DVM, PhD, DACVIM (Cardiology), the Randall B. Terry Distinguished Professor of Comparative Medicine and Associate Dean of Research. "Remember, dogs that carry the mutation also carry other important genes that we do not want to lose from this breed."

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The lead investigator of the ARVC gene mutation discovery, Dr. Meurs says, "Variable penetrance is poorly understood. We can identify which Boxers have the striatin-deletion gene mutation, but we cannot predict the penetrance. Further, there is likely more than one cause, so even if a dog is genetically negative, it does not mean the dog cannot get ARVC. Multiple genetic and non-genetic factors may contribute to the identical clinical disease."

Boxer ARVC is a heart muscle disease attributed to a deletion mutation in a gene that produces striatin, a key binding protein of the cardiac desmosome responsible for the heart's electrical functioning and holding cells together. ARVC may manifest as congestive heart failure. Fluid accumulates in the lungs, known as pulmonary edema. Affected Boxers develop a cough, shortness of breath and lethargy.

Boxers with ARVC may develop a run of VPCs, or early contractions of the lower right ventricle of the heart causing disturbed electrical impulses. These impulses direct the heart to beat and to maintain a steady, regular rhythm. A dog having multiple, successive VPCs, or heartbeats without a corresponding pulse, is not able to produce normal, effective contractions. Ultimately, this results in decreased blood flow to the brain and other vital organs. A prolonged run of VPCs can lead to cardiac arrest and sudden death in otherwise healthy adult dogs.

"We found Boxers that were homozygous for the mutation, or had two copies of the gene deletion, developed a more severe form of ARVC based on Holter monitor testing. When these dogs had VPCs, they tended to have more of them," Dr. Meurs explains.

Holter monitor testing can detect VPCs in Boxers suspected of having ARVC. Because the arrhythmia is intermittent, it may not occur during a standard three-minute electrocardiogram test or show on an echocardiogram, an ultrasound of the heart. A Holter monitor test is used to provide information about heart rhythm over a 24-hour period and thus is more accurate at identifying affected dogs than a brief electrocardiogram.

"Because these dogs appear to have more significant disease and will certainly pass on the mutation to their offspring, if they are bred they should be crossed with a dog that is negative for the mutation," she says. "Over a few generations, a puppy that is negative for the mutation can be selected as the replacement for the breeding program."

As to the value of the ARVC DNA test, Dr. Meurs says, "Mutation testing should be used with health testing. Breeders should use this test as a tool to guide them. For example, they might decide to breed dogs with positive attributes that are heterozygous for the mutation and do not show signs of disease to mutation-negative mates. We do not recommend breeding Boxers with two copies of the gene mutation unless they are exceptional dogs, and then they should only be bred to mutation-clear mates."

Meanwhile, Dr. Meurs is currently working on a study to identify a second genetic risk allele associated with the development of ARVC in Boxers. The two-year study, which runs until April 2022, is funded by the American Boxer Charitable Foundation, and the AKC Canine Health Foundation administers the grant. The research involves looking at DNA samples from Boxers with confirmed ARVC that are negative for the striatin-deletion mutation.

DM Mutation & Incomplete Penetrance

Boxers are among over 40 breeds and mixed breeds with definitively diagnosed degenerative myelopathy in the breed population. Joan R. Coates, DVM, DACVIM-Neurology, professor of neurology and neurosurgery, and colleague Gary S. Johnson, DVM, PhD, of the University of Missouri, led the discovery of the autosomal recessive mutation in the superoxide dismutase 1 gene (*SOD1*) along with Kerstin Lindblad-Toh, PhD, of the Broad Institute of MIT and Harvard. The team found that the mutated gene in dogs is the same as the one causing some forms of familial amyotrophic lateral sclerosis (ALS), or Lou Gehrig's disease, in people.

A devastating disease that mimics other neurologic conditions, DM initially impairs a dog's hind limbs. Dragging or scuffing of the legs leads to decreased muscle control and weakness causing frequent falls and difficulty getting up. Within 11 months, dogs are paralyzed, as DM spreads through the nervous system, damaging the spinal cord, brain, nerves, and muscles. Boxers are usually around 9 years of age when signs are recognized, though a definitive diagnosis is not possible until a necropsy and histopathology are performed after death.

When the *SOD1* gene discovery was published in 2009 in the *Proceedings of the National Academy of Sciences*, the investigators stated that the mutation has an age-related incomplete penetrance. The longer an at-risk dog lives, the higher the likelihood of developing signs of DM. However, they noted they did not know the precise risk for dogs having two copies of the mutant *SOD1* variant to developing DM.

"Although the DNA test helps breeders make breeding decisions, it has diagnostic limitations because it is testing for a risk factor and does not provide definitive diagnosis," Dr. Coates says. "Results from genetic testing allow breeders to breed dogs that carry the SOD1 mutation to clear, healthy dogs to avoid producing affected dogs without reducing genetic diversity.

"We have not yet definitely documented DM by histopathology in Boxers that have tested carrier. DM has been only definitively documented in Boxers testing homozygous or at risk. We continue to collaborate with Dr. Lindblad-Toh to pursue research to seek

modifying genes that could influence an individual dog's risks for developing DM. We, too, believe that dogs that carry the mutation also carry other important genes that we do not want to lose from this breed."
