When an easy-to-use and inexpensive DNA genetic test for centronuclear myopathy (CNM) became available in 2005, it seemed only a matter of years before the debilitating muscle disease in Labrador Retrievers would begin to fade away. The genetic test provided a tool that would allow breeders to selectively choose breeding partners and avoid producing affected puppies. While the numbers of CNM carriers and affected dogs may be somewhat reduced, experts say it is too early to determine exactly how much change has taken place.

Aggressive educational efforts by the French researchers who identified the CNM mutation in the PTPLA (protein tyrosine phosphatase-like) gene helped to spread the word among breeders and veterinarians. Articles ran in a variety of training and show magazines and newsletters for Labrador Retriever enthusiasts. Presentations at club meetings and health clinics held at dog shows and field events also helped to communicate information about the disease and the mutation. Despite the educational efforts, it is estimated, based on informal conversations with U.S. veterinarians, that more than 50 percent of veterinary clinics still are not aware of the possibility of the CNM mutation in Labrador pedigrees, says Marilyn Fender, Ph.D., global communications coordinator for the CNM Project. “The staffs at these veterinary clinics are not familiar with the disease characteristics, let alone that there is a DNA test for the disease and related breeding cautions,” Fender says.

“Many breeders still do not realize when they have an affected puppy,” she says. “They assume it is an accidental birth defect. Since carriers appear normal, it is impossible to identify them without testing. A small portion of breeders do recognize affected puppies and fear that mentioning it will affect the sales of puppies with their kennel name. Additionally, there are breeders who simply are not willing to accept DNA testing as a useful option.”

Owners of Carriers Unaware

CNM was first described in 1976. In the early to mid-1990s, three National Retriever Champions, as well as National Finalists, field champions and amateur field champions, were identified as CNM carriers when they produced affected puppies. Fender owned one of these National Retriever Champions, NFC-AFC Storm’s Riptide Star. Due to their success in the field, these dogs were bred multiple times, passing the mutated gene to their offspring without their owners being aware. Carriers also were identified in bloodlines for conformation and pet Labradors, although in less frequency and with fewer affected litters.

About this time, Stéphane Blot, D.V.M., Ph.D., of the Alfort School of Veterinary Medicine near Paris, France, led the CNM research on affected French dogs. He changed the name to CNM from a long list of other names, such as Labrador muscular myopathy, that have been used to describe the disease to more accurately reflect a condition previously described in a rare group of myopathies in humans named CNMs. As a result, the Labrador Retriever became a relevant model to better understand CNM in humans.

Laurent Tiret, D.V.M., Ph.D., associate professor of physiology and therapeutics at Alfort, continued the research. The team’s first publication describing the discovery of the causative gene mutation for CNM was in 2003. The finding led to the noninvasive cheek-swatch DNA test to determine whether dogs are CNM carriers, affected or normal. The French Association Against Myopathies supported the research due to the similarities between the Labrador and human diseases.

In June 2005, Tiret visited the U.S. and opened CNM genetic testing to the public through a presentation he gave at the AKC National Amateur Retriever Championship Stake in Hibbing, Minn. About 200 retriever owners, handlers and trainers attended. Articles appeared in Retriever News, Retrievers ONLINE, a Canadian online publication for Labrador field competitors, and the Labrador Retriever Club newsletter.

Since then, the Alfort School has tested thousands of Labrador Retrievers from 18 countries. According to Tiret, about 17 percent of the tests indicated CNM carriers and CNM-affected Labradors. A CNM International Registry, often referred to as a “white list,” publishes the names of clear dogs tested at the Alfort School.

“This list is extremely useful and is consulted by interested viewers.
around 3,000 times a month," Fender says. "We are not able to list carriers or affected dogs due to legal restrictions. Though that information would be extremely helpful, confidentiality regarding carrier and affected dogs prevents this from happening."

Unfortunately, the prevalence of CNM is not precisely known because it is contributed voluntarily rather than from a scientific randomized sample. Complicating the ability to track disease statistics is that there is no way to use estimated data from the private laboratories that have sprung up internationally to test for CNM, Fender says. "Although it may be easier to go to a single diagnostic laboratory for testing for many diseases previously identified by various research laboratories, it is recommend-ed to work with the DNA researchers who identify any disease, not just CNM, as they devote full-time attention to following up on the disease and its evolution," she says.

Identifying CNM in Puppies

Puppies with CNM are almost indistinguishable from their littermates at birth. When they are 4 weeks old, they lack or show weak tendon reflexes and weigh significantly less than their littermates. Some of these signs could be caused by other diseases and thus are not sufficient for identifying affected puppies. The disabling condition sets in by 3 to 5 months of age when puppies begin to walk with an awkward gait and experience decreased exercise tolerance. Cold environments worsen their general muscle weakness. Clinical signs are progressive but generally stabilized by around 12 to 18 months of age. There is no recovery of the muscles, and no medications help. The DNA test for CNM enables early identification of puppies carrying one or two disease copies of the CNM gene well before they show clinical signs. Before the DNA test was available, a veterinarian relied on a muscle biopsy to identify Labrador suspects-ed of having CNM. An invasive and expensive technique, muscle biopsies are not commonly used. "Every puppy tested at Alfort with two CNM gene copies became affected, demonstrating the specificity of our test," Fender says. Some puppies with CNM are euthanized when signs appear. Others that are more mildly affected can live up to about 12 years with continual special care and environmental conditions. Weakness in the muscles of the esophagus can cause megaesophagus, a secondary condition that leads to eating problems. Pneumonia due to food particles getting into the lungs is a frequent cause of early death.

When Karen Goodman of Bloom-field, Mich., got her chocolate Labrador Retriever, "Godiva," the happy, playful puppy was an ideal companion. Before Godiva was 6 months old, she began drinking sloppily and became incontinent. Then, the young dog began regurgitating food with increasing frequency. Godiva’s condition waned and then a period of bad days," Goodman says.

Working with her veterinarian, Goodman submitted a cheek swab sample from Godiva for genetic test-ing, which confirmed that Godiva had CNM. "One part of me was glad that we finally knew what was wrong with her, but part of me was sad because there is no cure for the disease," says Goodman.

When Goodman learned that Godiva had developed megaesophagus, it was heartbreaking news. "This explained the regurgitation, but there was nothing that could be done to help her," she says. "Eventually, a feeding tube was used to give her nutrition. For the last two months of her life, Godiva regurgitated nonstop as the disease took over."

Finally, after three and a half years, Goodman decided to have her beloved Labrador euthanized due to the suffering. "It was the continuation of her suffering that made me realize the time had come to put her down," Goodman says. "My experience with Godiva was heartbreaking, but I was honored to have the time I had with her. She taught me a lot because of her bravery and spirit with all she had to handle."

An Autosomal Recessive Disease

Centronuclear myopathy is a simple autosomal recessive disease in which affected puppies inherit a copy of the mutated gene from both parents. A puppy that inherits a single copy of the inherited gene from one parent will be a carrier. A litter bred from two carriers produces 25 percent affected puppies, 50 percent carriers and 25 percent non-carriers. A litter bred from a carrier and non-carrier produces no affected puppies, but half are carriers. "The identification of CNM carriers enables breeders to screen litters for carriers and non-carriers before placing puppies," Fender explains. "Litters can be tested before they are 7 weeks old. Many puppy buyers would be happy to own a carrier that would never show signs of disease. For breeders, knowing the status of puppies can help decide which puppy goes to which home. Given the importance of litter testing, the Alfort CNM Project decided to apply a significant discount for litter testing."

Donna Green of Parker, Ariz., wishes more breeders took advantage of genetic testing. She received her black Labrador Retriever puppy as a gift. At 12 weeks of age, the dog was not able to hold her head up when carrying a retrieving bumper in her mouth, and she had an odd bunny-hopping gait in her rear legs.

When "Layla" was 6 months old, genetic testing confirmed that she had CNM. "I had hoped Layla would be a hunting companion," she says. "When I learned there was a genetic test for this disease that the breeder could have used to avoid having affected dogs, I was angry."

"On bad days, Layla’s front end collapses, causing her to fall and skin her snout. Sometimes when we’re on a walk, Layla must stop to take breaks before we’re able to carry on. Though she weighs 57 pounds, her normal weight should be around 70 pounds."

Current Research in Dogs & Humans

In humans, CNM has two modes of inheritance. The autosomal dominant form, diagnosed in adolescents and young adults, can leave sufferers wheelchair-bound. The autosomal recessive form, diagnosed in children, may cause curvature of the spine. The similarities between the Labrador and human myopathies make Labrador Retrievers with CNM good models for the human disease. Revenue generated from CNM test-ing at the Alfort School is channeled back into research. “The researchers are committed to the health of the canine gene pool as well as future therapeutic applications to dogs and humans," Fender says. "Over $250,000 in testing from U.S. breeders has come back into the research. This has enabled the Alfort scientists to identify in collaboration with other French and U.S. laboratories three other canine mutations in Staffordshire Terriers, Labradors and Great Danes."

In collaboration with an international consortium, the team also is exploring the role of PTPLA in human muscle pathophysiology, using unique cell and mouse models developed in part with the genetic testing money. "After years of active research, we now understand the biochemical function of PTPLA," Tiret says. "We hope to soon have opportunities to test new drugs to alleviate the damage done by CNM in cells, mice models and affected Labradors. Once efficacy and safety of these treatments are validated in animals, we hope to be able to treat humans."

Purina appreciates the support of the Labrador Retriever Club Inc. and particularly Fran Smith, D.V.M., Ph.D., DACT, the LRC health chair-woman, in helping to identify topics for the Purina Pro Club Labrador Retriever Update newsletter.

Want to Reach the Editor?

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