Researchers Seek Candidate Genes for Protein-Losing Enteropathy

Researchers at Cornell University School of Veterinary Medicine in Ithaca, N.Y., are working to find candidate genes that predispose Yorkshire Terriers to protein-losing enteropathy (PLE), a potentially fatal condition in which dogs lose significant protein into their gastrointestinal system.

While genetics are likely to play a role in determining which dogs are predisposed to developing PLE, environmental factors, such as enteric (intestinal) bacteria or food intolerance or allergy, may contribute as well. The extent to which environmental factors influence the disease is not fully known.

In Yorkshire Terriers, PLE is widely attributed to lymphangiectasia, a condition in which the lymph vessels become dilated and disrupt the normal flow of lymph throughout the body. Recent studies have shown extensive cystic dilatation of the intestinal crypts (mucosal glands of the epithelial lining of the small intestine) also may contribute to PLE. One study showed that Yorkies have a tenfold greater risk of developing lymphangiectasia than other breeds.

Recognizing the widespread occurrence of PLE in the breed, the Yorkshire Terrier Club of America and the Yorkshire Terrier Club of America Foundation recently helped fund an AKC Canine Health Foundation grant that supports the Cornell University research. The researchers’ ongoing efforts to collect DNA samples from affected and normal dogs are instrumental to the success of the study.

“Our goal is to identify a gene change or set of changes that predispose a dog to PLE,” says lead investigator Nate Sutter, Ph.D., assistant professor of medical genetics. “The evidence that PLE has a genetic component primarily rests on the observation that some breeds — such as Yorkies — are at an elevated risk for the disease. The simplest explanation is that at-risk breeds have one or more genetic factors that confer risk.”

Ultimately, once a genetic marker is identified and the causative mutation for PLE is discovered, a DNA test can be developed that would identify affected dogs and thus provide a diagnostic tool for the disease. Currently, the only definitive test to detect and distinguish between different causes of PLE is an intestinal biopsy that is expensive, requires general anesthesia and carries some health risks.

The severity of PLE varies among individual dogs and may be related to differences in genetic expression of the disease. Some dogs show no clinical signs, yet die quickly. Others exhibit serious manifestations, but with proper disease management do well. Diarrhea, anorexia, vomiting, lethargy, weight loss, edema (swelling) or ascites (fluid in the abdominal cavity), and respiratory difficulty from fluid in the chest are not uncommon signs in dogs with PLE.

Other at-risk breeds for PLE are Basenji, Chinese Shar-Pei, Norwegian Lundehund and Soft-Coated Wheaten Terrier. The genetic basis for the disease may vary by breed. Besides lymphangiectasia, conditions that can occur in Yorkshire Terriers include peritonitis, or inflammation of the membranes lining the abdomen. After seven months, Youngblood made the difficult decision to have Taffy euthanized.

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Pancreatitis was the initial diagnosis given Denise Fallon’s Yorkie, “Winnie,” who had lost her appetite and frequently vomited. After two weeks on a bland diet, Winnie continued to weaken. Fallon, of Mechanicsburg, Pa., was referred to a veterinary teaching hospital, where the specialist recommended an intestinal biopsy to determine definitively whether Winnie had PLE.

Only weeks after the first signs of PLE, Winnie died of peritonitis following the intestinal biopsy procedure. “It was probably a result of the disease causing changes that weakened the intestinal walls,” Fallon says.

“Chloe,” a 12-year-old Yorkshire Terrier owned by Jane Downey of Columbus, Ohio, continues to thrive despite having been diagnosed with PLE when she was 9 years old. “I have to work hard to keep Chloe’s weight down with a strict diet,” Downey says. “She loves to get into the other dogs’ food bowls, so it’s a constant struggle. If she overeats, she gets bloated.”

Another long-lived Yorkshire Terrier diagnosed with PLE is “Martha,” a retired conformation champion belonging to Stephanie Ruiz of Orange County, Calif. Martha was diagnosed at age 9 and today is 15. “When we were still working on a diagnosis, we tried several diets for Martha, but none seemed to help,” Ruiz says.

Once Martha was definitively diagnosed with PLE, the veterinarian prescribed medications to help manage signs of the disease. “The key for us is consistently following the veterinarian’s instructions regarding diet and medications,” says Ruiz. “Martha’s protein level is normal, and she has lived longer than any Yorkie we have ever owned.”
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lead to PLE are inflammatory bowel disease, intestinal lymphoma and fungal infections such as histoplasmosis.

Dogs with PLE lose protein from the body through the intestines. Normally the intestines absorb dietary protein from food during the digestive process, but the reverse happens in dogs with PLE. In these dogs, the protein is released into the intestines and lost in feces.

Signs of a Similar Condition

Chronic, occasional vomiting was common in Julie Fritz-Rubert's 4 1/2-year-old Yorkshire Terrier, "Phoebe." When the dog vomited six times in one day, she became concerned. A few days later, the dog's abdomen appeared bloated. "I took Phoebe to the veterinarian, who suspected she had gastroenteritis but ran blood work to be sure," says Fritz-Rubert of Sacramento, Calif.

The blood test showed that Phoebe had low levels of albumin and globulin, consistent with PLE. The veterinarian recommended an intestinal biopsy to determine definitively whether Phoebe had lymphangiectasia or another cause of PLE. The biopsy confirmed that Phoebe had mild to moderate lymphangiectasia.

The lymph vessels in Phoebe's body were dilated due to pressure from inflammation. The lymph vessels in the intestines, called lacteals, were not able to absorb dietary fat because of increased intraluminal pressure with subsequent malabsorption of fat and other nutrients such as fat-soluble vitamins. With the loss of nutrients, particularly protein and fat, Phoebe had begun to lose weight.

Disease management focused on reducing inflammation in the intestinal mucosa and fluid accumulation in the abdomen. A corticosteroid, prednisone, was prescribed for the inflammation, and an immunosuppressive medication, azathiaprine, was given to control overaggressive immune responses.

Dogs diagnosed with PLE may be given medications such as tylosin or metronidazole, which also help to modulate bacteria that may promote inflammation and reduce the risk of thromboembolism, a blood-clotting disorder that is common in dogs with PLE, and a low-dose diuretic may be given to reduce intra-abdominal fluid.

Veterinarians often recommend feeding a low-fat diet enriched with medium-chain triglycerides rather than the long-chain triglycerides found in most dietary fat. The shorter chain triglycerides may be absorbed directly into the bloodstream, bypassing the lymph system.

Even with medications and a special diet, Phoebe's abdomen was enlarged for about six weeks. "We could tell she didn't feel well," Fritz-Rubert says. "At first, she didn't eat well, even with the prednisone. We could see she was wasting away and was losing muscle mass. We could see the bones in her shoulders and feel her spine. We were so afraid we would lose her."

After a couple of weeks, the veterinarian increased Phoebe's prednisone. "It was like magic," says Fritz-Rubert. "Over five days, Phoebe went from weighing 7 pounds to 5 pounds, and she lost 4 inches around her belly. The weight loss was because her ascites improved."

Several months after Phoebe was diagnosed with PLE, good news came on a veterinary visit. "It turned out Phoebe had gained too much weight," Fritz-Rubert says. "Her big belly was due to fat, not fluid as we had feared."

Not only had Phoebe gained weight, but her albumin and globulin levels were normal. The toy dog regained muscle mass and began feeling good, even playing. Phoebe continues to take a small dose of prednisone and is fed a low-fat diet and low-fat treats. She also continues to take the immuno-suppressive medication, azathiaprine, which clearly states on the label: Give medicine every other day, forever.

How to Contribute to PLE Genetic Research

Breeders and owners of Yorkshire Terriers can contribute DNA samples to help advance genetic research at Cornell University. "We are trying to identify candidate genes that cause protein-losing enteropathy (PLE). The researchers are requesting samples from affected dogs of all ages and from older, healthy dogs. For information about the criteria to qualify and how to submit samples and pedigree and clinical information, please contact Dr. Kenneth Simpson at kws5@cornell.edu or 607-253-3567, or Dr. Nate Sutter at sutterlab@cornell.edu."

Phoebe's DNA will be included in the study. Fritz-Rubert became an advocate for supporting the genetic research while learning about the disease through Phoebe. "I probably have spent about $4,000 in medications and veterinary visits for Phoebe," she says. "The emotional toll has been just as costly."

When she found an online forum (http://www.saveolive.com/phpBB3/) for people whose dogs suffer from PLE, Fritz-Rubert welcomed the comfort of sharing her experiences with others. "I discovered this while Phoebe was in the hospital," she says. "I have learned so much from reading other people's stories. We have lost lots of dogs to this, and each one breaks my heart."

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