fig. 56

Pet Detective

MU's College of Veterinary Medicine is, as one expects, all about how to better breed and feed food animals and care for companion animals. But the college is also building its reputation for translational medicine. Its stable of genetics researchers has a lot to say about human health and treating human diseases. Story by Erik Potter • Illustration by Jen Lobo

It starts like a stale joke. What do you call a blind, epileptic dog that walks into a veterinary clinic?

For Gary Johnson, associate professor of veterinary pathobiology, there isn't just one answer. Such a dog is a mystery, a research opportunity, an adventure, a chance to improve the lives of both dogs and people. In short: It's his life's work.

Just such a canine arrived at the MU Veterinary Medical Teaching Hospital in summer 2014, piquing Johnson's interest. Johnson is part of a team of clinicians and researchers in the College of Veterinary Medicine; the College of Agriculture, Food and Natural Resources; and the School of Medicine that finds cures and treatments for neurological diseases that affect animals and humans.

Johnson has used whole-genome sequencing to discover more disease-causing mutations in dogs than all the other laboratories combined, says collaborator Martin Katz, professor of ophthalmology in the School of Medicine.

Johnson's work begins after veterinary hospital clinicians find a dog with a compelling genetic disease and after the symptoms have been studied and described. His job is to uncover the genetic cause of the illness.

"I could have retired five years ago with full benefits," Johnson says. "But I'm having too much fun."

Johnson is a genetic sleuth. If you likened the genome to a city street map, his job would be to discover the exact house and the room the bad guy sleeps in with just a few street names as clues.

And if Johnson is inclined to see every pooch and pup as a string of DNA base pairs and polynucleotides, it's because he has already cracked the genetic code of 11 canine maladies, including neuronal ceroid lipofuscinosis, a neurodegenerative disorder; Fanconi syndrome, a kidney disorder; and paroxysmal dyskinesia, a condition responsible for abnormal movements and posture.

Once Johnson identifies the mutation, others develop treatments to cure or alleviate it.

"All the diseases we've found so far have had human counterparts," Johnson says. In other words, treatments developed for dogs might also help humans.

The process works like this: Our blind, epileptic dog is taken to the veterinary hospital. The clinician recognizes the dog as an important case and tells Johnson, who has DNA from the dog's blood sample sent to MU's DNA Core Facility for genome sequencing. There, using commercial software, Bob Schnabel, research associate professor of animal sciences, identifies every variant on each of the animal's genes. With 20,000 genes and multiple variants for each, that list can reach into the millions. Schnabel filters the findings to yield only variants in genes that could possibly cause the condition in question, which normally cuts the list to around 60,000.

The list goes to Johnson, who consults his canine DNA database and rules out variants that are missing from similarly diseased dogs or that appear in healthy dogs. This cuts the list to about 60 variants, perhaps five of which have been associated with the disease type being investigated. Then Johnson heads to the lab and runs assays on the DNA of other dogs with and without the disease to verify that they do or don't have the same variant as the dog they just sequenced. "If only the affected dogs have the variant ... then that's our proof," he says.

Once Johnson identifies the disease's genetic cause, the action moves to researchers to develop treatments. Collaborators include Joan Coates, professor of neurology and neurosurgery, small animal medicine, and surgery in the College of Veterinary Medicine, and Katz.

For 20 years, Johnson and Katz have worked on Batten disease. A degenerative neurological condition, the disease affects both dogs and people. The mutations that underlie Batten disease prevent the normal breakdown and removal of waste products in neural cells. The waste gradually accumulates and impairs neurological function. The disease is almost always fatal.

When Johnson and Katz started their research, only three forms of Batten disease were recognized in people. Today, scientists recognize many forms, each caused by mutations in at least 13 genes. Johnson and Katz have identified mutations in eight of those genes in dogs with Batten disease.

Dogs with these mutations can serve as models for the corresponding human disorders. Using one of these dog models, Katz is developing two treatments for Batten. One involves bimonthly injections of functional waste-disposal enzymes into the cerebrospinal fluid. Neural cells take up the enzymes, which can restore some waste-disposal function and blunt the progression of the disease. Based on success with the dog studies, human trials are underway. The second, less-developed method involves inserting a normal form of the waste-disposal gene directly into the cells of the brain.

Katz is effusive in his praise of his colleague. Johnson is an unassuming, avuncular man. He will never tell you how otherworldly good he is at what he does, Katz says.

"He's brilliant," he says. "He's humble, but believe me — he's brilliant." **M**