When Good Dogs Get Bad Genes

It was a formality, really. The barrage of health clearance tests before "Daphne" had her second litter in 2007 was just something that all responsible Golden Retriever breeders did. So when the ophthalmologist peered into Daphne's eyes, her owner, Mardi Closson of Schnecksville, Pa., was unconcerned — until he said Daphne had progressive retinal atrophy (PRA).

Closson was in disbelief. Daphne's vision seemed fine. She was competing in agility. Besides, PRA was uncommon in Goldens.

According to Kaye Fuller, D.V.M., a member of the GRCA (Golden Retriever Club of America) Health and Genetics committee, CERF (Canine Eye Registration Foundation) examination scores from 1990 to 2005 indicated that only 39 Goldens, or about 0.05 percent, were affected with PRA.

Closson immediately sought a second opinion from Gustavo Aguirre, Ph.D., V.M.D., professor of medical genetics and ophthalmology at the University of Pennsylvania School of Veterinary Medicine. He confirmed the diagnosis.

PRA has several different forms caused by different mutations. The most common form is progressive rod cone degeneration (*prcd*), found in more than 25 breeds. But the 20 or so Goldens that had been previously DNA-tested for *prcd*-PRA had come back negative. When Daphne's positive DNA results came back from Optigen testing labs in Ithaca, N.Y., it was a second shock. She was the first Golden ever diagnosed with *prcd*-PRA.

"Daphne," a Golden Retriever who was diagnosed with progressive retinal atrophy in 2007, helped increase awareness of the disease. At right, Daphne earns the Masters Agility Champion title.

Some breeders may have been inclined to hide the test results, but Closson, along with Daphne's co-breeder, Gerry Clinchy, went public, spearheading efforts to investigate *prcd* in Goldens.

"Our first conversation was about how we should proceed. We discussed getting related dogs tested, talking with folks, then a discussion with Optigen and the Golden Retriever Club of America about the best way to share information and encourage more dogs to get tested, not just dogs directly related to Daphne," recalls Closson.

The GRCA held DNA collection clinics at its National Specialties. Clinchy and other Golden fanciers created a database (*www.goldendna.com*), where owners can list their dogs' genetic status as clear, carrier or affected.

So far, of 919 Goldens tested for *prcd*-PRA, five have tested as affected and 196 as carriers. Among the carriers are Daphne's offspring from her first litter, which now are successful competition dogs themselves. In the past, being a carrier of PRA was enough to be culled from most responsible breeding programs.

"When I decided to breed my Daphne daughter, I got some 'Nos' in the beginning from stud dog owners, including some with advice that I should throw this line away and start again," says Closson.

This was common advice before DNA testing, but now geneticists advise that's exactly what you shouldn't do. In line with current thinking, Closson

Decreasing the Incidence of Hip Dysplasia

DNA tests are especially informative for diseases caused by single recessive alleles. But many disorders, such as hip dysplasia, are caused by the combined action of several genes, along with environmental influences.

The Orthopedic Foundation for Animals (OFA) in Columbia, Mo., cautions breeders not to discard a dog as potential breeding stock because he has a "fair" hip classification. In fact, because of the polygenic basis of hip dysplasia, a dog with fair hips coming from a canine family with a strong hip background is actually a better breeding prospect than a dog with excellent hips coming from a weak family background.

OFA recommends these breeding principles:

- Breed normals to normals;
- Breed normals having normal ancestry;
- Breed normals having siblings with a low incidence of HD;
- Select sires producing a low incidence of HD; and
- Replace dogs for breeding with dogs that are better than the breed average.

Recommendations are generally breed-dependent. "Breeders of some breeds probably should not use fairs whereas other breeds may need to breed mildly dysplastic dogs," says G.G. Keller, OFA chief of veterinary services. "It depends on how the hips of an individual dog and his family compare to the rest of the breed."

The OFA has seen dramatic improvement in hip scores since its founding in 1966. Breeds with the greatest numbers submitted, including Rottweilers, German Shepherd Dogs, Golden Retrievers and Labradors Retrievers, have shown the most progress.

bred the daughter to a clear male, tested the offspring for carrier status, and kept a clear puppy for possible future breeding.

As for Daphne, she went on to become MACH Pine Run A L'il Daph'll DoYa, WC, AAD, OD, ADHF, OF, earning the Masters Agility Championship title in 2007. Now her vision is fading, and she's been retired from agility. Her titles combined with those of her offspring have earned her a place in the GRCA Hall of Fame, but her long-term contribution to the breed will doubtless be one she will never get a title for — the ability to nip an emerging disease in the bud.

As Closson says, "I've found the bright side of this by concluding that Daphne is special and has done something very special for the breed. It wasn't bad breeding that brought us here, but it is bad breeding if we hide from it or refuse to deal with it and share the information honestly."

The Puppy & the Bath Water

The Golden Retriever community has met the announcement of *prcd*-PRA in their breed by being active, but not overreactive. The *prcd*-PRA gene has been found in at least eight unique carriers. Only a decade or so ago, the announcement of affected or carrier status would spell the end of a breeding career, possibly an entire line, in an effort to cull the mutant gene from the population. Today's breeders learned their lesson at the expense of yesterday's breeders.

Take the case of the Portuguese Water Dog (PWD). Two distinct lines — Algaborium and Alvalade — formed the basis of PWD stock in America. In the 1980s breeders became aware of a fatal lysosomal storage disorder called GM1-glangliosidosis in American PWDs. Fortunately, a blood assay test identified carriers with over 95 percent accuracy. The Portuguese Water Dog Club of America worked with geneticists to promote a "breed and replace" strategy, in which high-quality carriers could be bred to normal testing mates, after which the carrier parent would be replaced for breeding with a normal testing offspring. This strategy would allow the good qualities of the carrier to be passed on, limit depletion of the gene pool and still select against GM1.

But many PWD breeders balked at the idea of using carriers. If a little selection was good, a lot would be better. As DNA testing made available in 1999 allowed dogs with the GM1 gene to be identified with certainty, it became clear that the GM1 gene originated from the Algaborium line, while the Alvalade line was clear. Breeders abandoned the Algaborium line in favor of Alvalade dogs. GM1 carrier numbers plummeted; from 1999 to 2006, the carrier rate was about 2 percent, without a single report of an affected PWD.

Unfortunately, some PWDs were going blind. Testing revealed that the Alvalade line carried the *prcd*-PRA gene. By then, the carrier frequency for *prcd*-PRA was higher, 35 percent, than the carrier frequency for GM1 ever was, 6 percent. Because breeders had virtually abandoned the Algaborium line, which didn't carry the *prcd*-PRA gene, they had essentially traded one problem for another.

Sue Pearce-Kelling, president of Optigen, says that breeders are often dismayed to the point of overreacting when a disease is identified in their breed. Advice from breed clubs having experienced this is reassuring.

Portuguese Water Dog

"Once it becomes clear that the DNA test will allow them to continue to breed any of their dogs and still be assured of avoiding disease, they realize they can retain the good qualities and gradually move away from the disease over time," says Pearce-Kelling. "If they want to breed a dog that carries a recessive mutation, they simply need to choose a mate that does not carry that mutation,

and then choose 'clear' offspring from that generation or a following one."

It Takes Two

The ultimate goal, of course, is to eradicate bad genes. "While the best way to prevent a disease from plaguing a breed is to eventually eliminate all the disease-causing versions of a gene from the population, care should be taken to do so gradually," says Robert Loechel, chief scientific officer at Vetgen DNA testing in Ann Arbor, Mich.

"Of course, 'It depends' is always my answer to nearly any question. In the case of extremely rare and severe diseases, I would suggest eliminating the disease allele whenever possible. In other cases it would be impractical because the mutant allele is very common, and the disease itself is often very mild."

Doberman Pinscher

When the Optigen DNA test for *prcd*-PRA became available in 1998, Australian Cattle Dogs had an affected rate of 22 percent and a carrier rate of 48 percent. Cattle Dog breeders knew they couldn't remove every carrier from breeding without inviting potentially worse problems, so they carefully bred to avoid producing affected dogs rather than to remove the gene from the population. Thus, their carrier rate is still high at 49 percent, but their affected rate is down to 8 percent.

A similar situation exists with the bleeding disorder type 1 von Willebrand's disease (vWD) in Doberman Pinschers. Before DNA testing, blood factor screening yielded so much overlap in results between clear and carrier Dobermans that carrier status was questionable. Once the gene was found, breeders could confidently identify carriers.

In just over 10 years, the percentage of affected (homozygous) Dobermans fell from 30 percent to 19 percent, and the disease allele fell from 55 percent to 42 percent. The fact that the disease incidence has fallen at a much greater rate than the allele incidence suggests breeders are using carriers, but not breeding them to one another or to affected dogs.

Even when dealing with a disease as serious as degenerative myelopathy (DM), a progressive spinal cord condition that often results in paralysis, compromises may be necessary. A DNA test for DM was developed in several breeds last year, but this doesn't mean the condition will be quickly eradicated.

Tapping into Frozen DNA

To advance genetic research requires DNA samples. Keep in mind, even if a dog has died, DNA testing may be possible from frozen semen. Approximately 6 to 10 million sperm cells — about a half a straw or a few pellets — are needed, and they need not be motile or frozen for analysis.

According to Liz Hansen, project coordinator at the Animal Molecular Genetics Laboratory at the University of Missouri College of Veterinary Medicine, "There is such a high prevalence of the mutation for DM in Boxers and Pembroke Welsh Corgis that carrier to carrier, and even affected/at risk to carrier may be valid choices. It's taken many generations to get into the current situation, and it will take several generations to get out of it and keep the breed in good shape, maintaining genetic diversity, breed type and other positive traits."

Progress differs from breed to breed and disease to disease, depending on a number of factors. Corgis and Poodles, for example, can also have type 1 vWD. Unlike Dobermans, neither breed has lowered its affected or carrier incidence significantly probably because the incidence was so low to start with that most breeders don't prioritize it.

When breeders prioritize a disease, impressive progress can be made. Ten years ago copper toxicosis (CT), a copper storage disorder, was widespread in Bedlington Terriers. A liver biopsy was the only way to diagnose it early. When VetGen found a marker gene that was closely linked to the CT gene, it allowed better, but not totally accurate, prediction of carriers.

A marker gene is one that's located so close to the mutant gene that the two tend to be inherited together. In this case, about 90 percent of Bedlingtons with two copies of the marker gene had CT. When the actual gene for CT was discovered a few years later, carriers could be identified with total accuracy. Affected dogs went from 52 percent down to 12 percent in 2008, with gene frequency dropping from 67 percent to 32 percent. In this case breeders have primarily selected against producing affected dogs, but have also gradually reduced the incidence of the gene.

As Loechel points out, these data don't necessarily represent the breed as a whole, but only those dogs from the subset of people who test their animals. In breeds with fewer dogs, such as Bedlingtons, it's comparatively easy to get the word out about diseases and DNA testing.

"In the Bedlington Terrier," he says, "there was tremendous awareness before the test was available, followed by a significant amount of 'drumbeating' after its availability by some very dedicated breeders. We see dedicated folks in every breed, but with a smaller number of animals in a breed, and thus a smaller number of breeders, each of these people has a relatively louder voice."

All dogs carry undesirable recessive genes, many for devastating diseases. DNA testing allows carriers and affected dogs to be bred because it makes it easier to avoid producing affected dogs.

Fuller, the veterinarian who is a member of the Golden Retriever Health and Genetics committee, brings up another caveat about eliminating particular genes. "The possibility exists that on a particular 'bad' gene, there may be a trait that is highly desirable — perhaps resistance to developing cancer, for example. Even with the advent of some new DNA tests, the art of breeding dogs and the path to the 'perfect mating' may not be as straightforward as we would hope." ■