PRA IN GOLDEN RETRIEVERS

… A Breeder's Challenge

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(This is not meant to be a definitively technical article. Rather, it is an explanation of a breeding concept, in layman's terms.)

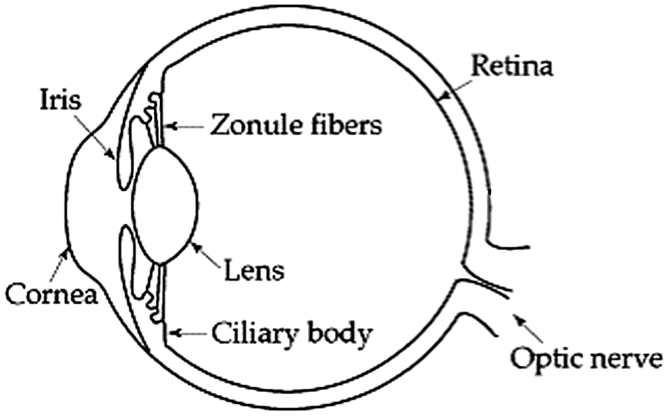
In January 2007, a Golden Retriever was diagnosed with physical evidence of Progressive Retinal Atrophy (PRA) as a result of a routine eye examination at a club-sponsored eye clinic. The examiner commented that he did not think he had seen a case of PRA in a Golden Retriever in ten years, and thought the disease was nearly extinct in Golden Retrievers. With this in mind, a second opinion was recommended.

The dog was taken to Dr. Gustavo Aguirre for a second opinion. For those who may not know, Dr. Aguirre, together with Dr. Gregory Acland, while both were working at Cornell University, did the definitive research and development of today's DNA testing procedure for the prcd-PRA gene. Their initial data was published in March 1998 (just 10 years ago!). By license from Cornell Research Foundation, the DNA test they developed is now available through Optigen®, LLC, located in Ithaca, New York. The original test available was a genetic marker identification. Today, however, the test has been refined to actually locate the mutant gene that is the cause of the disease. This refinement is more accurate than the original marker test.

Upon confirmation of the physical diagnosis by DNA test, those involved proceeded to provide samples for Optigen testing of both parents of the affected dog. The parents were confirmed as carriers. Additional samples were provided of closely related dogs. The results of testing indicated that the mode of inheritance followed the predicted pattern that had already been demonstrated in other breeds. The prcd-PRA gene is identical in all the breeds in which it has been identified.

Further, Optigen seeks to cooperate with the national breed clubs of the breeds who utilize their DNA testing. Thus, GRCA was notified of this information, and contact was made with Optigen by the GRCA Health & Genetics Committee. One goal of this cooperation is to encourage genetic testing of any affected dogs that are accurately diagnosed with physical evidence of PRA. Optigen provides testing of affected dogs at no charge. This policy applies to all breeds, as well as Golden Retrievers.

Up until the testing of this Golden Retriever in early 2007, test samples had been submitted to Optigen for testing from several (though not many) other Golden Retrievers who had physical evidence of PRA. Those tested may have been of either U.S. or European origins. The prcd-PRA gene was *not* found in these other Golden Retrievers. When the diagnosis of inherited PRA is firmly credible, and when the prcd-PRA gene is *not* detected, the advice given is to stop the breeding program. As there is no way to predict how the unidentified gene will be transmitted to progeny, there would be high risk of producing progeny with visual impairment.

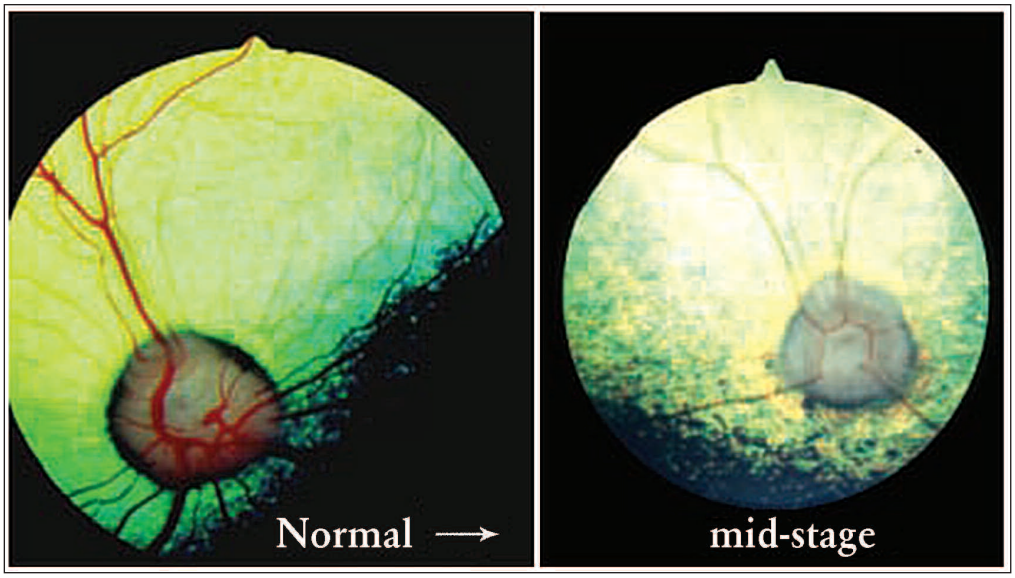


Light enters the eye through the pupil. The iris acts like the shutter on a camera to determine how much light will enter. The cornea and lens focus and invert the image so it can be projected onto the back of the eye to the retina. The cells of the retina convert the light signal into a neural signal. The "rod" and "cone" cells are the actual photoreceptors. The ganglion cells of the retina transmit the light signal to the brain through their axons which make up the optic nerve.

The cones are the cells that work in bright light for visual acuity. The rod cells are most sensitive to low light and dominate in peripheral vision.

The conclusion is, thus, that there is at least one other gene that occurs in Golden Retrievers that can cause PRA. The prcd-PRA gene is not the *only* one. This is also the case in Mini and Toy Poodles.

Over the course of time, small numbers of U.S. Golden Retrievers, from the recollection of various breeders, were known to have had PRA. These dogs go back many years. They are not really useful in studying the problem now. With no genetic testing available then, there is no way to determine if their PRA was



Canine Eye with mid-stage PRA. Photos courtesy of Dr. Gustavo Aguirre.

accurately diagnosed as inherited, or whether it was the prcd-PRA gene that caused their disease. There is also some belief that CPRA (central PRA, where the center of the retina is affected first) may have been a result of nutritional deficiency, and all but disappeared as commercial dog foods came into near-universal use. Not enough is known about those early occurrences to speculate how they relate to the present. Dr. Aguirre firmly believes that there is no evidence that CPRA is anything but a nutritional disorder, and should not be considered further in any discussions or recommendations on inherited retinal diseases.

Almost all of the technical information mentioned in this article is available at the Optigen website, *www.optigen.com*. You may also have to use the links to various websites of individual breeds to get some additional details. It is worth reading this information to have the best understanding of this problem.

Upon request, a staff person at Optigen, LLC provided statistics about the general incidence of PRA in Golden Retrievers. Among eye examinations performed by ACVOs (American College of Veterinary Ophthalmologists) on Golden Retrievers from 2000 to 2005, only .05% were diagnosed to have physical evidence of PRA. That was about 20 dogs total. Doing the arithmetic, that 20 dogs came from 33,000 to 34,000 examinations. This is, indeed, a very small incidence. Of course, 20 affected dogs mean there were at least 40 carriers of the gene needed to produce the 20 affected. (As a recessive gene, both parents would have to be at least carriers in order to produce an affected progeny.)

Even so, by mid-2007, another carrier of the prcd-PRA gene was located via Optigen's DNA testing which was *not* related to the original family of dogs in which the gene was first detected.

Please note that Optigen maintains absolute patient confidentiality. Results of testing are never given to anyone but the owner of the dog tested. However, the owner(s) of the dog(s) can then share that information with others. In the Portuguese Water Dog community, the public sharing of Optigen test results is as common as our sharing of OFA hip results. Labrador Retrievers have a voluntary database of Optigen test results as well.

PRA is a general term: Progressive Retinal Atrophy. As the name would imply, the retina of the eye gradually degenerates, and most dogs afflicted will eventually be blind. The disease can be further subdivided by specific reference to "prcd", which stands for progressive rod-cone degeneration. It is this type of PRA which has been found to occur in about 20 different breeds of dogs. Those most familiar to most people would be Labs, Chessies, and the Mini and Toy Poodles.

Nightblindness is the first symptom of the disease that might be noticed by an owner since the rod cells of the retina are the first to lose function. The rod cells are those which function in low light. However, an examination by a veterinary ophthalmologist could detect the onset of the disease before the owner might notice any symptoms.

Not all retinal disease may be PRA. Physical distinctions between inherited PRA and other eye diseases are important. Therefore, it is highly useful to have annual eye exams by a veterinary ophthalmologist to assure accuracy of diagnosis. Cataract formation is also a secondary sequel to PRA**.** However, we must not confuse this secondary cataract formation with inherited cataracts in Goldens which are caused by a defect in a different gene. Dr. Aguirre is currently researching the mode of inheritance of inherited cataracts in Golden Retrievers.

The prcd-PRA gene has behaved as a simple recessive mode of inheritance. It is possible to "manage" this gene within a breeding program, or within a breed, by using carriers, clear, and, for the brave of heart, even affected dogs. The DNA testing can be performed on young puppies before they leave for new homes if so desired. Yes, even an affected dog can be bred to a clear dog with no risk of visual impairment to the progeny. All the progeny, however, will be carriers as the affected parent has only a "defective" gene to contribute.

Judicious use of carriers is done with Portuguese Water Dogs, a rare breed. You can see this if you visit the litter listings on the website of the Portuguese Water Dog Club of America (*www.pwdca.org*) Available litters listed there include Optigen test results, along with other health screening information. It may be obvious that with the very small gene pool of a rare breed, such management would be a necessity. It may not be as obvious why a breed as numerous as Golden Retrievers would also choose to use carriers as breeding stock.

Recent advances in the technology of genetics indicate that genes for unrelated traits may be present on the same piece of genetic material. Elimination of an undesirable gene may also eliminate a desirable gene. Once the genetic material has been lost, it is gone forever.

Consider the situation that already has come to light in Golden Retrievers. The undesired prcd-PRA gene was located in one area of the gene pool. We eliminate all those related dogs who may be carriers, along with all their other genetic material. Then another carrier is located in another area of the gene pool. Again all carriers are eliminated, along with their other genetic material. After several years, this process could be replicated several times. Each time that the process eliminates the undesirable gene, other genetic material is also being discarded – forever. As time progresses and other diseases are discovered, the genetic material that has been discarded might have been the very thing needed to do battle with the new disease.

Be careful what you wish for! How often have people said, "If we only had a DNA test for …"? You got your wish. Now it will require thoughtful care to utilize the tool. It will challenge breeders to make even more complex decisions in their breeding programs.

There are also some tried-and-true guidelines validated by this new information. Since symptoms for PRA in Goldens can be as late as six years of age, annual physical eye examinations are the first line of defense. These examinations should include not only breeding stock, but also as many siblings of breeding stock as possible. Since carriers will never be detected by physical examination (as they will never manifest the disease), it could be that "pet puppy" out there who might be affected would give the first clue that there are carriers present in the breeding program. With a late age of onset and gradual deterioration of vision, a pet owner might not consider an inherited disease like PRA as a reason for their pet's decreased vision at age eight or nine.

Physical eye examinations into later years can assure that these dogs are not affected with PRA. The worst they could be are carriers. If an affected dog should turn up, and you are trying to do pedigree research, it could be helpful to know which ancestors had normal eye exams later in their lives.

Breeders will be challenged to wrap their minds around the concept of using dogs that have a known genetic flaw (carrier status or even affected), but yet have merit to contribute to a breeding program. Dr. Aguirre states: "It is always important to keep in mind that you are breeding dogs, and not test results when dealing with DNA-based testing. Dogs of exceptional merit that contribute to the breed, genetic diversity and gene pool of the breed should be bred, and the test results used only to select the appropriate mate. The aim is never to produce an affected dog, and, at the same time, maintain the genetic diversity of the breed."

This is a whole different concept from what Golden breeders are used to working with. Every past and present health screening done up till now evaluates phenotype, *not* genotype.

We should not confuse this DNA test with the blood testing done for VWD many years ago. While the VWD test was a blood test, it was not accessing genotype. The test was simply evaluating physical evidence of certain blood factors, more complex than a simple blood count, but still not a genotype test. While blood is used for the prcd-PRA testing, it is a far different kind of testing. (Cheek swabbing can also be used, but if done incorrectly, may not gather enough genetic material for testing.)

One can use hip dysplasia as another example that is very familiar to Golden breeders. Hip x-rays are an evaluation of physical evidence (phenotype), but it is *not* looking at the genes themselves. Every time a Golden with "normal" hips is bred, we are guessing that the physical evidence we can see is an accurate representation of its genotype (genetic make-up). If this were truly so, breeding an OFA "Excellent" to an OFA "Excellent" should produce 100 percent normal offspring every time. This has not proven true in reality. No one has yet tapped into a "snapshot" of the genes that result in hip dysplasia (which is believed to involve more than one set of genes).

Breeders will also be challenged to share the information of a dog's carrier status. Their colleagues will be challenged to accept this disclosure as a sign of conscientious care by those who do the sharing. Many already have found that a responsible breeder can do "the right thing," and end up with a mess. It is so much better to clean up the mess, rather than sweep it into a dark corner, where someone else can come along and step in it.

Sources:
Optigen® website; *www.optigen.com*
Portuguese Water Dog Club of America website; *http://www.pwdca.org/*
Personal correspondence with Optigen® staff
Personal correspondence with Gustavo Aguirre, VMD, PhD

This article was approved by the GRCA Health & Genetics Committee.