

Breakthroughs for Golden Retriever Health:

Finding Genes for Progressive Retinal Atrophy and Ichthyosis

by Ann F. Hubbs DVM, PhD

Progressive Retinal Atrophy – GR_PRA1

Big news from the 2010 Advances in Canine and Feline Genomics Conference in Baltimore, MD – *researchers now believe that there are three different genetic conditions that can cause progressive retinal atrophy (PRA) in Golden Retrievers.* PRA is a clinical disease characterized by retinal degeneration and blindness. In affected dogs, PRA can be diagnosed when fully developed by a veterinary ophthalmologist, but that is often in a mature dog that may have been bred many times. It can be diagnosed earlier using electroretinography. Since 2008, a genetic test for one form of PRA, prcd-PRA has been available (Hubbs, online; Optigen, 2010a). Prcd-PRA is a recessive genetic disease meaning that an affected Golden must have two abnormal copies of the prcd-PRA gene to get PRA. Both genetically affected dogs and unaffected carriers of this genetic condition can be identified by DNA testing at any age, including in young puppies.

At the genomics conference on September 24, Louise Downs of the Animal Health Trust in the United Kingdom, and her colleagues announced the identification of a new form of PRA that affects Golden Retrievers (Downs et al, 2010). This new form of PRA is also caused by a recessive mutation and caused 70 percent of the PRA cases in their study. Recently, the Animal Health Trust has made the resulting DNA test commercially available. In the supporting literature, they report that their research suggests that the mutation causing this new form of PRA, tentatively called GR_PRA1, is found in roughly 5 percent of the Golden Retrievers in the UK, but less than 0.5 percent of the Golden Retrievers from the US (Animal Health Trust). Louise Downs and colleagues also reported that still another genetic condition appears to cause some cases of PRA in Golden Retrievers but that gene has not yet been identified.

Ichthyosis

The big news for Golden Retrievers continued at the conference – *researchers now report the identification of a genetic mutation causing ichthyosis in Golden Retrievers.* Ichthyosis is a scaling skin disease. In people and dogs there are actually many different kinds of ichthyosis, and Golden Retrievers get at least one form of the disease (Mauldin et al, 2008; Guaguere et al, 2009; Cadiergue et al., 2008; Oji et al, 2010). In one report, the uncoated skin of the belly of affected Golden Retrievers was reported to have increased pigment and to be rough to touch (Guaguere et al, 2009). The clinical expression of the disease ranges from severe cases (large blackish scales with multiple infections), to mild cases (very small scales on the

body to scales only localized in certain parts of the body). The mild cases might be clinically unnoticed. Although ichthyosis does occur in U.S. Golden Retrievers (and over the past two years, multiple breeders with affected Golden Retrievers have contacted the GRCA Health and Genetics Committee), the incidence appears to be very low.

On September 25, 2010, at the genomics conference, Catherine André of the School of Medicine, Rennes, France, reported that her laboratory has identified the gene that causes ichthyosis in Golden Retrievers (Grall et al, in preparation). In addition, she reported that ichthyosis is inherited in



Images of the skin of Golden Retrievers with ichthyosis provided courtesy of Dr. Catherine André and Dr. Eric Guaguere.



Images of the skin of Golden Retrievers with ichthyosis provided courtesy of Dr. Catherine André and Dr. Eric Guaguere.

the breed as an autosomal recessive disease, requiring that each parent of an affected dog have at least one copy of the abnormal (mutated) gene. In France, roughly 30 percent of Goldens are affected (have two copies of the mutated gene), 40 percent of Goldens are carriers (have one copy of the mutated gene), and 30 percent of Goldens are normal. Very recently, in the course of the study led by André and collaborators, the same gene has been found to be mutated in two human families presenting with a similar ichthyosis form, segregating with an autosomal recessive transmission mode. An international patent has been deposited for the identification of the mutation and its use for diagnosis in Golden Retrievers and an international license is held by Antagene. A DNA test for the identified mutation, ICT-A, is commercially available in Europe and can identify Golden Retrievers that are affected, healthy or carriers (Antagene, online). On December 16, Optigen announced that they will make this test available for U.S. Goldens (Optigen, 2010b).

Inheritance of ichthyosis and GR_PRA1

As noted above, ichthyosis and GR_PRA1 are believed to be inherited as autosomal recessive conditions. Since autosomal recessive conditions develop when a dog receives a gene for that disease from *each* parent, the results of genetic tests for autosomal recessive conditions fall into three categories:

1. Normal – these dogs have two copies of the normal gene

(homozygous normal), no copies of the disease gene and have no known risk for producing puppies with the tested condition. In short, these dogs look normal (phenotypically normal) for the condition and are genetically normal for the condition.

2. Carriers – these dogs have one copy of the normal gene and one copy of the disease gene and can produce affected puppies if bred to a carrier or a genetically affected dog. In short, these dogs do not appear to be affected with the condition but they have one gene that is mutated. If bred to homozygous normal dogs their offspring will also not be affected but half will be carriers.
3. Affected – these dogs have no copies of the normal gene – both copies of the gene for this condition are mutated. These dogs are genetically affected and usually phenotypically affected. Importantly, for later-onset diseases like some forms of PRA, these dogs look normal in early life but the disease manifestations appear late.

In many ways, U.S. Golden Retriever owners and breeders are fortunate since we have a basic understanding of inherited diseases in the breed through long standing health testing for normal hips, elbows, eyes and hearts. We now have DNA tests for three autosomal recessive diseases that can serve as an introduction to basic dog genetics in real life. We have genetic tests for *prcd*-PRA, GR_PRA1, and ichthyosis. Each of these can be viewed as recessive diseases that come very close to classic Mendelian genetics. The two phenotypically normal Goldens (Sire and Dam in the chart below) that each carry one copy of the normal gene (shown here as N) will not show outward evidence that they carry an abnormal gene (shown here as n for not normal) because expression of the mutated gene is obscured by the normal gene. However, when the two carriers are bred to each other, the two alleles (one copy of a gene pair) sort randomly into the offspring and the classic Mendelian Square looks like this:

| | | Sire | |
|-----|---|------|-----------|
| | | N | n |
| Dam | N | NN | Nn |
| | n | Nn | nn |

Roughly one in four of the offspring from two carriers will have only the abnormal genes (shown here as nn for in the lower right cell of the table outlined in bold) and will develop the disease.

It is important for breeders to understand that other genetic tests are also available for Golden Retrievers and many more will become available over the next few years. For one of the existing tests, degenerative myelopathy (available through OFA), two copies of the abnormal gene appear to make these dogs “at risk” for degenerative myelopathy, but many of these dogs actually remain healthy (Awano et al, 2009; University of Missouri, online). Thus, degenerative myelopathy is very similar to the simple autosomal recessive conditions explained above except that two copies of the disease gene do not appear sufficient to cause degenerative

myelopathy and additional research will be needed to find out what else contributes to development of that disease. Another test available to Goldens is a linkage test for Hemophilia A, a sex-linked recessive bleeding disorder. A linkage test does not test for the actual mutated gene, but instead tests for a marker located so close to the disease gene that they are usually inherited together (Brooks et al, 2005).
Implications of the New PRA and Ichthyosis Tests

Owners of Golden Retrievers with PRA and scaling skin diseases now have genetic tests that may help identify the cause of their conditions, but since these diseases currently appear to be uncommon among U.S. dogs, at this time it is not necessary for all breeders to add these DNA tests to routine pre-breeding screening examinations. However, dogs with a first degree relative (parent, sibling, or offspring) that either has the disease or has been DNA tested as a carrier should be tested prior to breeding. These tests allow carriers to be bred to homozygous normal Goldens so that healthy puppies are produced. However, the offspring of affected and carrier Goldens should also be tested before they are bred. Those importing Golden Retrievers or breeding to Goldens from countries where the condition is common may also find the tests helpful in assuring healthy puppies.

As caretakers of the breed, we need to be thinking about and discussing in advance the appropriate use of DNA testing to protect both individual dogs and diversity in the gene pool, as genetic tests become widely available for many different conditions in our breed. It is especially important to keep carrier status in perspective because as more genetic tests are discovered we will undoubtedly find that all Golden Retrievers carry some deleterious genes. Breeders need to feel safe to test their dogs and make results public, knowing that positive findings do not need to automatically eliminate dogs from breeding.

To put this in perspective, there are no genetic tests available yet for many widespread conditions with a heritable component in Golden Retrievers – including hemangiosarcoma, lymphosarcoma, osteosarcoma, hip dysplasia, elbow dysplasia, subvalvular aortic stenosis, cardiomyopathy, swallowing disorders, cataracts, aggression, epilepsy and pigmentary uveitis. We expect the time for those genetic tests is not far away. In fact, ongoing research at the Broad Institute into inherited risk factors for canine cancers has identified at least five genes of interest in the development of hemangiosarcoma (www.dogdna.org). If additional research proves that each of these genes can be associated with hemangiosarcoma in Golden Retrievers, it is likely that a large percentage of our dogs have one or more genes that contribute to the risk of hemangiosarcoma.

It is also very likely that as we begin to understand the inheritance of a spectrum of genetic diseases in Golden Retrievers, many of these will be much more complicated than *prcd*-PRA, *GR_PRA1*, and ichthyosis. However, it is also likely that we can look forward to a day when we have a panel of tests that will allow us to more accurately understand and manage the risk for a prospective breeding. The result will be Goldens that live longer, healthier lives.

References and Online Resources

- André, C et al. A new human ichthyosis gene revealed by the identification of a mutation in the golden retriever canine breed. Presented at the Advances in Canine and Feline Genomics Conference, September 25, 2010. Baltimore, MD.
- CNRS/University of Rennes1, France; Canine genetics projects: <http://dog-genetics.genouest.org>
- Animal Health Trust. Progressive Retinal Atrophy in the Golden Retriever. Online test information available at: https://secure.ahdnatesting.co.uk/documents/versions/35_uv8cYt23.pdf
- Antagene. Ichthyosis Golden Retriever ICT-A test. Online test information available at: <http://www.antagene.com/uploadfichier/Anglais/ICT-A.pdf>
- Awano T, Johnson GS, Wade CM, Katz ML, Johnson GC, Taylor JF, Perloski M, Biagi T, Baranowski I, Long S, March PA, Olby NJ, Shelton GD, Khana S, O'Brien DP, Lindblad-Toh K and Coates JR. Genome-wide association analysis reveals a SOD1 mutation in canine degenerative myelopathy that resembles amyotrophic lateral sclerosis. *Proc Natl Acad Sci USA* 2009 Feb 24; 106(8):2794-9.
- Broad Institute. Dog disease research at Broad Institute. <http://www.broadinstitute.org/scientific-community/science/projects/mammals-models/dog/disease-research/dog-disease-research-broad>
- Brooks MB, Barnas JL, Fremont J, Ray J. Cosegregation of a factor VIII microsatellite marker with mild hemophilia A in Golden Retriever dogs. *J Vet Intern Med.* 2005 Mar-Apr;19(2):205-10.
- Brooks MB, MacNguyen R, Hall R, Gupta R and Booth JG. Indirect carrier detection of canine haemophilia A using factor VIII microsatellite markers. *Anim Genet.* 2008 Jun;39(3):278-83
- Downs L, Boursnell M, Bergström T, Lindblad-Toh K, Marklund S, Hedhammer A, Truvé, Wallin-Håkansson B, Hübner L, and Mellers C. A novel mutation is associated with progressive retinal atrophy in the golden retriever. Presented at the Advances in Canine and Feline Genomics Conference, September 25, 2010. Baltimore, MD.
- Guaguere E, Bensignor E, Küry S, Degorce-Rubiales F, Muller A, Herbin L, Fontaine J, André C. Clinical, histopathological and genetic data of ichthyosis in the golden retriever: a prospective study. *J Small Anim Pract.* 2009 May;50(5):227-35
- Hubbs A. An Update on Eye Disease in Golden Retrievers Part 1: Progressive Retinal Atrophy. Available online at: <http://www.grca.org/health/retinalatrophy.html>
- Mauldin EA, Credille KM, Dunstan RW, Casal ML. The clinical and morphologic features of nonepidermolytic ichthyosis in the golden retriever. *Vet Pathol.* 2008 Mar;45(2):174-80.
- National Human Genome Research Institute, Canine Genomics Research. Genetics Primer for Owners. http://research.nhgri.nih.gov/dog_genome/info_for_dog_owners/primer.shtml
- Oji V, Tadani G, Akiyama M, Blanchet Bardon C, Bodemer C, Bourrat E, Coudiere P, DiGiovanna JJ, Elias P, Fischer J, Fleckman P, Gina M, Harper J, Hashimoto T, Hausser I, Hennies HC, Hohl D, Hovnanian A, Ishida-Yamamoto A, Jacyk WK, Leachman S, Leigh I, Mazereeuw-Hautier J, Milstone L, Morice-Picard F, Paller AS, Richard G, Schmuth M, Shimizu H, Sprecher E, Van Steensel M, Taïeb A, Toro JR, Vabres P, Vahlquist A, Williams M, Traupe H. Revised nomenclature and classification of inherited ichthyoses: results of the First Ichthyosis Consensus Conference in Sorèze 2009. *J Am Acad Dermatol.* 2010 Oct;63(4):607-41.
- Optigen (2010a). The OptiGen *prcd*-PRA Test. Available online at http://www.optigen.com/opt9_test_prcd_pra.html
- Optigen (2010b). DNA Test for Ichthyosis (ICT-A) in the Golden Retriever. Available online at http://www.optigen.com/opt9_ichthyosis_gr.html
- University of Missouri. Degenerative Myelopathy: Test for Degenerative Myelopathy Gene NOW AVAILABLE! <http://www.caninegeneticdiseases.net/DM/ancmntDM.htm>