

MORE ABOUT PRA (PROGRESSIVE RETINAL ATROPHY)

INTRODUCTION: Progressive Retinal Atrophy has been consistently identified by veterinarians and purebred dog owners as being one of the most widespread categories of canine genetic disease. Despite concern about and awareness of the disease, PRA has resisted eradication. One of the distinguishing features of the disease is the unpredictability of both the age of onset and the rate of loss of eyesight in affected dogs, as well as which dogs will be affected.

Work by Aguirre, Parshall and others has demonstrated that "early onset" PRA has a breed-specific basis. There is also evidence, however, that late onset PRA is mediated by genes which are common in several breeds. Based on the information produced from their research, a basis now exists for the gradual elimination of PRA in purebred dogs. An understanding of the underlying genetic nature of the different forms of PRA is a prerequisite for the use of an appropriate screening system. The ideal system would predict both later development of the disease in puppies and the elimination of carriers from the breeding population.

THE COMPLEX STRUCTURE OF THE EYE: Hereditary retinal degenerations in the dog comprise a diverse and complex group of genetic diseases collectively known as Progressive Retinal Atrophy (PRA). PRA cause gradual loss of vision, often leading to total blindness. PRA has been recognized in a large number of dog breeds (40-80). In only a few of them has PRA been characterized in detail. Some well-characterized disorders appear to be breed-specific and within each breed have characteristic clinical and genetic properties.

Within a breed, PRA is most frequent among offspring of crosses of two affected dogs, or an affected dog and an apparently unaffected dog, although it is also found in the progeny of healthy parents. The pattern of transmission from generation to generation in families suggests that the disease is primarily caused by defective versions of genes that specify vital steps in the development or function of the retina.

Many genes regulating different biochemical and developmental pathways are participating in the complex structure and function of the eye. Any one of the pathways is susceptible to being affected by inherited deleterious genes. That complexity helps to explain why there is a diverse range of manifestations in the time of onset, severity, and time for full development of PRA.

Therefore, PRA should be considered as a heterogenous group of genetic diseases which can be mediated by many independent genes.

CLASSIFICATION OF DISTINCTIVE FORMS OF PRA: In many dog breeds PRA has not been well characterized clinically, pathologically and genetically. So far, there are at least two types of hereditary PRA which have been adequately studied: the early onset, or developmental type and the late onset, or degenerative type.

The gene is recessive, which means that, to be affected, a dog must inherit two copies of the defective gene, one from each parent. A dog that inherits the defective gene from one parent and the normal gene from the other parent becomes an unaffected carrier that can transmit the defective gene to the next generation.

DIAGNOSIS AND ERADICATION OF PRA: Breeders often choose to mate closely related animals. There is then an increased likelihood that defective gene pairs will be inherited from carrier parents. As a consequence, genetic diseases caused by single recessive genes are more likely to occur in domesticated animals than in humans. Health problems which are mediated by single gene pairs are known as "simple" diseases. Dog breeders can work toward elimination of simple diseases by isolation of affected dogs, scrutiny of pedigree records and test breeding of suspected carriers. As with all genetic diseases, the way to prevent inheritance of simple eye disease is to eliminate the faulty genes from the breed, by preventing mating of both affected dogs or carriers of defective genes.

Occurrence of an affected pup in a litter indicates both sire and dam are carriers for the simple autosomal trait, and they should not be used for further breeding.

CONDITIONS WHICH COMPLICATE DISEASE CONTAINMENT: Those PRA variants which have been relatively well studied indicate that specific, but distinct single recessive genes occur at the breed level. Even if every case of PRA were caused by specific pairs of single genes, the task of identifying carriers and defining the route of inheritance for affected dogs would be a complicated one.

The unpredictability of the age of onset and the rate of deterioration of eyesight in PRA-affected dogs does raise the question of whether more than one gene has a significant impact on the course taken by each variant of PRA. This possibility also needs to be borne in mind in analysis of PRA in dogs at the molecular genetics level.

DIAGNOSIS OF PRA IN AFFECTED DOGS WITH ERG: Most of the time, deterioration of vision due to PRA does not become evident until a dog is old enough to have been bred. There is an urgent need for a way to determine, in puppies, if the animal will develop PRA or if it carries a recessive defective gene that can cause PRA in its descendants.

The disease can be diagnosed in the affected dogs by means of ophthalmoscopic analysis in the early-onset PRA, between the age of 6 months to 2 years, depending on the breed. The late-onset form of PRA cannot be detected in this way, in most cases, until the animal is 3-4 years old. However, PRA can be detected earlier by recording the retinal response to different types of light through a technique called electroretinography (ERG).

This technique is, at present, the best one available for early diagnosis of PRA. However, ERGs are not easy to do and they require specialized equipment and training. This procedure is expensive and it does not detect carriers of defective recessive genes. In approximately 60% of recorded PRA cases, affected dogs show no symptoms until their seventh year or older. If the individual gene could be identified which causes PRA, then puppies could be screened as early as the first week to detect those which would be carried and/or affected. Thus breeders could put down affected pups, sell carriers without breeding rights, and keep clear puppies for future breeding.

IDENTIFYING THE CARRIERS OF PRA: With the introduction of ERG, a basis now exists for gradual progress towards elimination of PRA. Instead of waiting for the expression of defective genes or depending on a diagnostic method which has a appreciable error rate, a method is needed for determining if defective genes are present, regardless whether they are expressed, i.e., functioning, or not.

A rich pool of polymorphic marker candidates at the DNA level offers the prospect of being able to correlate the genes responsible for a complex trait by associating a distinct marker for a complex trait by associating a distinct marker with each genetic component of the trait. Multiple DNA markers can be expected to provide, for the first time, a means of detecting components of undesirable traits, including genetically complex inherited diseases, thereby offering a means to eliminate them through breeding. [I understand this is still some years away. A.M.]

EXPERIENCE WITH GENE TRACKING IN HUMANS: In recent years, enormous progress has been made in the understanding of the genetic and biochemical basis of many genetic diseases of humans. DNA markers have been found for a rapidly growing list of genetic diseases of humans, and the positions of these markers in the genetic map of humans has been determined.

These scientific and medical advances have raised hopes for success in the development of DNA marker methods for early detection of genetic diseases in dogs. While large amounts of money are spent on research on the mechanism and control of human genetic diseases, relatively little is spent on genetic research of animals.

[This article condensed from "USING DNA TO CONTROL PRA" by John A. Stuebaker, Sent in by Sharon Michael. Thanks.]

Pat Roder was one of the first to suggest that there is a problem with PRA in Dachshunds, and to admit that she indeed co-owns a dog with PRA (see December 1991 Digest). I recently asked her for some comments on how she proposes to deal with the problem and she graciously submitted the following for our Digest readers. Thanks, Pat! A.M.

HOW TO COPE INTELLIGENTLY, WHEN PRA STRIKES YOUR KENNEL

Now that we have discovered PRA (Progressive Retinal Atrophy) in our Standard Wire line, and possibly in our Miniature Long line as well, where does one go from here? The tears have already been shed, annual testing is now a normal part of our lives, and we hope we are acting for the betterment of the breed.

In announcing a problem well over a year ago, at that time it appeared that Dick & I and a few other breeders associated with our line, were crying wolf. PRA was not a problem in Dachshunds, hence, we don't have it. My dogs were the rarity. Subsequently, we have learned that this is not the case. In my opinion, what needs to be done by all reputable breeders, is to take one's ego out of the situation. It really doesn't matter whose line has been afflicted with PRA--whether it's been a successful breeder who has many wins to their credit, or the novice breeder--what is important is that our main concern is for the betterment of the breed.

I have been told that PRA is a simple recessive, hence we should be able to breed it out of our lines. I have successfully bred out crooked tails in my miniatures, by labeling one dog as suspect, and avoiding that particular animal in a pedigree. Whether or not that will hold true for generations to come, I don't know, for until science gives us an actual gene for that problem, we won't know if it is there or not. The same holds true for PRA. At the present time, my dogs (living with me) have tested clear, however, I am still labeling all of them carriers, and breeding accordingly. I am outcrossing, which I needed to do anyway, for other aspects I needed in my dogs, but only to those whose dogs have been tested. That still does not guarantee that I will not be breeding a carrier to a carrier, however, it should minimize the risk.

Since this problem is relatively new to our breed, we do not have a track record to fall back on. I have been told not to eliminate the quality animals that may be carriers from my breeding program altogether, as then we may run the risk of losing all the aspects of a quality Dachshund.

I hope that those of you that attended DCA, took advantage of the blind/blind PRA clinic that Dr. Morris offered. Each breeder has to decide for themselves whether or not they will announce that PRA is in their line. In our case, the dogs that we breed are for ourselves, and we may not breed a whole lot of litters down the road. However, if we do, our clients, both show & pet, will definitely be notified of a potential problem, and testing will be a part of any sale contract.

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