Papillon Club of America Health & Genetics

WHAT IS PRA ?

By Dr. Simon Petersen-Jones

Progressive retinal atrophy (PRA) is the name given to a group of conditions that are inherited and result in a progressive loss of vision leading to blindness. The disease targets the photoreceptors in the retina. These are the cells that convert the picture formed on the retina at the back of the eye into electrical messages that are conveyed to the brain, the retina being the equivalent of the film in a camera.

Several different forms of PRA occur with each different form being caused by a different gene mutation. PRA is described in many breeds of dog, with one survey reporting that over 100 different breeds may suffer from it. It is known that some forms of PRA affect more than one breed of dog, for example the progressive rod cone degeneration (prcd) form of PRA is known to affect several different breeds. However, other forms of PRA seem to be breed-specific.

It is therefore difficult to predict how many different forms of PRA exist. Research into retinitis pigmentosa in humans, which is the human equivalent of PRA, shows that there are over 30 different forms and over 130 genes known to cause hereditary retinal diseases of all forms. We can expect that dogs suffer from a many different forms of PRA. The retina is a complex structure and its formation and continued function are controlled by a large number of genes.

Potentially mutations in any of the genes that govern retinal structure and function could cause a disease such as PRA. The potentially large numbers of different forms of PRA makes studies to detect the gene mutation that causes the disease in any one breed difficult.

INHERITANCE PATTERNS OF PRA

The majority of forms of PRA are inherited in an autosomal recessive manner, although dominant and X-linked forms have been identified. Autosomal recessive diseases require that both copies of the disease gene are abnormal for the dog to develop the disease itself. Thus one abnormal copy of the gene is received from the dam and one from the sire. Dogs that have one abnormal copy and one normal copy are described as carriers. Carriers do not develop the disease themselves but they will pass on the abnormal gene to approximately 50% of their offspring. This has the effect that the condition will skip generations. Recessive diseases are particularly difficult to eradicate without a genetic test.

Where there is no genetic test carriers can only be identified by test mating with a known affected animal and seeing if the offspring become affected. To stand a very good chance that the test dog is not a carrier several clear offspring must be produced from the mating with the known affected dog. To achieve the required number of offspring more than one litter may be needed. For diseases that cannot be diagnosed until the affected dogs are several years of age test-mating is not a practical proposition. Diseases that cannot be diagnosed until the affected dogs are several years of age have the added complication that affected dogs have often been bred from before the diagnosis is made.

THE AFFECT THAT PRA HAS ON A DOG

PRA causes a loss of the cells in the retina that detect light (the photoreceptors). Photoreceptors come in two main types; rods for dim light vision, and cones for bright light color vision. With PRA the rod photoreceptors die first followed by the cone photoreceptors.

Therefore the affected dogs lose nighttime vision initially followed by daytime vision, until they are totally blind. The onset and speed of vision loss varies between the types of PRA. Some forms result in night-blindness in puppies followed by total blindness in the first few years of life, whereas other forms have an onset in middle-age and result in blindness several years later.

Owners may notice that the pupils of a PRA-affected dog seems more dilated than those of their other dogs. There is also an increased reflection of light from the back of the eye (eye shine) that is made more obvious by the more widely dilated pupils. Secondary cataract is common with the later-onset forms of PRA. Indeed owners will assume that the loss of vision is due to the formation of cataracts. Veterinary ophthalmologists will always rule out the presence of PRA prior to performing cataract surgery on a dog.

EYE EXAMINATIONS TO DETECT PRA

Regular eye examinations are useful in detecting PRA. The changes the ophthalmologists can see are an increased reflection from the tapetum of the eye. The tapetum is a highly reflective structure in the wall of the upper part of the back of the eye. It underlies the retina and reflects light back through the retina to help increase vision in dim light. The tapetum is responsible for the colored reflection seen from the eyes of animals caught in a car's headlights. When the retina becomes thinned due to PRA it allows even more reflection of light back from the tapetum.

This appearance is described as tapetal hyperreflectivity. The next change the ophthalmologist looks for is a thinning of the blood vessels that overlie the retina. Because the retina is dieing these blood vessels that supply the retina do not need to supply so much blood. The vessels transmitting less blood look thinned. This can first be seen in the smaller blood vessels.

ELECTRORETINOGRAMS TO DETECT PRA

The electroretinogram is a technique for assessing the function of the retina. When a flash of light is shone into the eye it triggers electrical activity in the retina. This response, the electroretinogram (ERG), can be recorded at the surface of the eye. The ERG can be a sensitive detector of early generalized retinal dysfunction and can therefore be useful in the early diagnosis of PRA. It is important to realize that there are different standards of ERG. The sort of ERG that is commonly used by veterinary ophthalmologists to check that that the retina is functioning before removing a cataract is quite different from the detailed ERG needed for early detection of PRA.

General anesthesia and a quite extensive protocol measuring responses to flashes of different light intensities and sometimes different colors of light is required for early PRA detection. The ERG responses vary a lot between different breeds of dog and with age, so to detect early changes in the ERG tracings due to the early stages of PRA it is important that the normal responses for the breed and age of the dog are already known. This means that a database of normal ERG responses needs to be established for the breed prior to detecting early PRA changes.

DNA-BASED TESTS TO DETECT PRA

There are two main categories of DNA-based test for PRA. The gold standard is the mutation detection test. This is a test that detects the presence or absence of the PRA causing gene mutation. Obviously this first requires that the PRA causing mutation is identified. When trying to identify the gene causing mutation its position may be mapped to a particular chromosome and a DNA marker identified that is closely linked to the location of the disease causing gene.

It can still be a lot of work to move from the linked marker to identify the PRA causing gene mutation. While this work is being completed it may be possible to use the linked marker for a DNA test. An example of this sort of marker test is currently available for the prcd form of PRA. This test can be used to divide dogs into three groups.

The first group only contains normal dogs. The second group contains carriers and some normal dogs while the final group contains all the affected dogs but also some carriers and some normal dogs. This is helpful so long as a dog in the first group is available; because this dog can be mated with any other dog and the offspring will not develop prcd.

However it is possible that the offspring could be carriers of prcd, depending on the status of the other parent. This sort of linkage based test obviously has its limitations but is better than having no test at all.

PRA IN PAPILLONS

A large survey in Sweden showed that PRA could be diagnosed by eye examination in some Papillons at under two years of age. Early diagnosis of PRA by eye examinations can be difficult in some Papillons because they have a poorly develop of absent tapetum. This is a normal variation, but makes it impossible to detect tapetal hyperreflectivity, meaning the diagnosis of PRA must be made on the basis of retinal blood vessel attenuation; this feature is not usually obvious in the earlier stages of PRA when tapetal hyperreflectivity has already developed. An electroretinographic study showed that abnormalities in the electroretinogram could be detected from 1½ years of age.

RESEARCH INTO PRA IN PAPILLONS

The aim of our study is to investigate a series of candidate genes and candidate loci to see if PRA in the Papillon is due to mutations at any of the selected candidate genes or loci. With forms of PRA, like that in the Papillon where the retina appears to develop normally and then goes on to degenerate it is essential to investigate the prcd locus.

Prcd is a form of PRA that is known to affect several different breeds and has been mapped to canine chromosome 9, although the actual gene that causes prcd has not been identified. We have used markers to show that PRA in Papillons does not map to the prcd region of chromosome 9 therefore showing PRA in Papillons is not prcd. We are also developing markers within several genes that are candidates for PRA and using those markers to see if PRA in Papillons can be mapped to the same chromosomal location as those genes.

The markers that we are developing are usually what are called single nucleotide polymorphisms (SNPs, pronounced "snips"), this is where there is a difference of one of the basepairs that makes up the DNA of the gene between different individuals. When a SNP is close to the PRA causing gene for that particular breed all the PRA-affected dogs will be homozygous for the SNP. Homozygous means that both of their two copies of the gene have the same version. We have currently obtained DNA samples from many PRA-affected Papillons and are using this to see if any of our candidate genes are potentially the site of the disease-causing gene mutation.

The candidate genes we have chosen to investigate are those known to cause PRA-like diseases in humans of experimental mice, or genes that we know are important in the function of the retina. All the genes that we have investigated so far have proven not to be the site of PRA in the Papillon. We intend to continue checking genes and have drawn up a list of about 100 gene loci to investigate and are hopeful that one of our candidates will prove to contain the mutation that causes PRA in the Papillon.

The hardest part of these studies is finding the gene mutation that causes the PRA, once it has been identified developing a DNA-based test to identify carriers of PRA is relatively easy.