

# Screening for Progressive Retinal Atrophy in Tibetan Terriers

## What is PRA?

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 similar number of 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

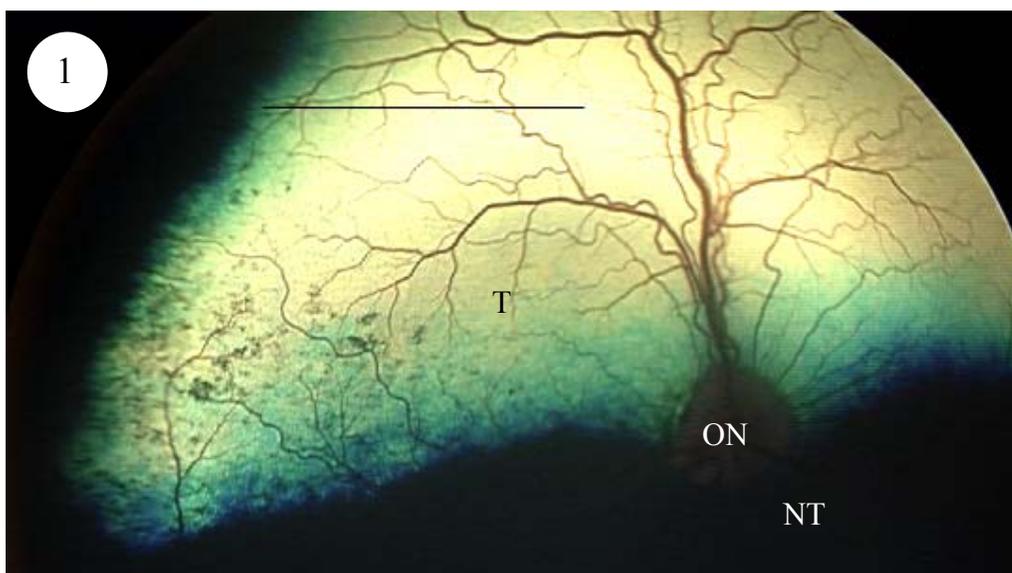
The majority of forms of PRA are inherited in an autosomal recessive manner, as in the Tibetan Terrier, although dominant and X-linked forms have been identified in other breeds of dog. Autosomal recessive diseases require that both copies of the disease gene are abnormal for the dog to develop the disease 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 to identify the genetic status of breeding animals. When PRA cannot be diagnosed until after breeding animals are sexually mature eradication is even more difficult because affected dogs may have been bred from before it is realized that they are affected. Until a genetic test is available it is important that a veterinary ophthalmologist examines all breeding animals for early signs of the condition prior to breeding. Even after a test is developed eye examinations should still be performed to allow identification of different emerging genetic eye diseases.

## 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 typically 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. In Tibetan terriers the onset of vision loss is in early middle age.

Owners may notice that the pupils of a PRA-affected dog seem more dilated than those of their other dogs. There is also an increased reflection of light from the back of the eye (eye shine), a change that is made more obvious by the more widely dilated pupils. Secondary cataract is common with the later-onset forms of PRA. Indeed owners sometimes wrongly 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.



**Figure 1. Wide-angle view of back of a normal dog eye.**

**T** - the tapetal fundus, this is the brightly colored area that ranges in color from yellow to green to blue at the periphery.

**NT** – the nontapetal fundus. This is darkly pigmented. In this photograph it is more difficult to see the details in this part of the fundus than of the reflective tapetal area; this is because the exposure was set to show the tapetal fundus.

**ON** – optic nervehead. This is where the nerves from the retina come together to transmit information about vision to the brain.

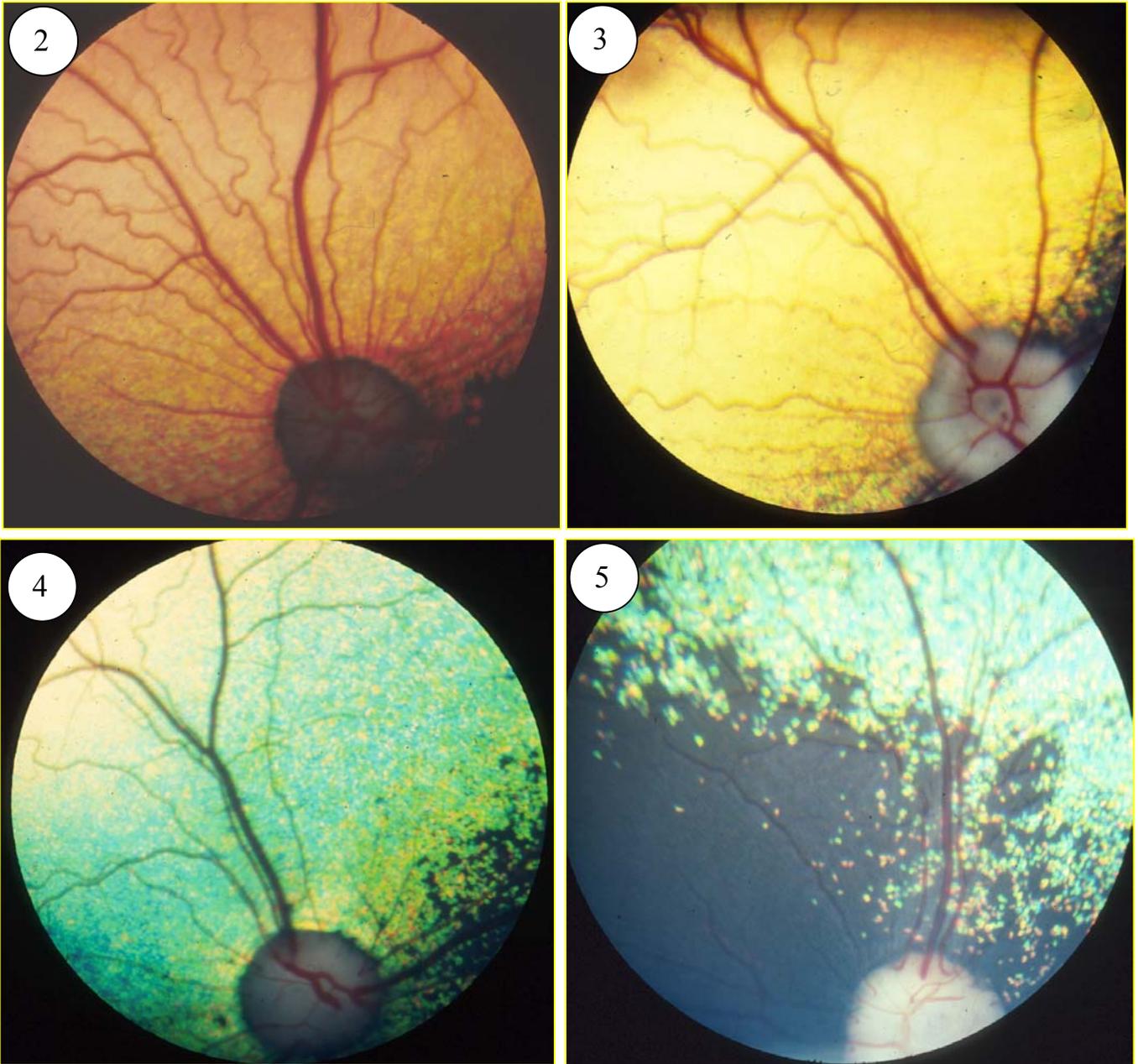
Note the red lines which are blood vessels that radiate over the retina from the optic nerve head. They also course over the nontapetal fundus, although they cannot be seen in this photograph

## **Eye Examinations to Detect PRA**

Regular eye examinations are useful in detecting PRA. Changes are visible in the eye as the retina dies and becomes thinner. Most dogs have a reflective structure in the top part of the fundus (fundus is the name for the back of the eye – see Figure 1). 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 (see Figures 6 & 7). Prior to obvious tapetal hyperreflectivity a subtle almost granular appearance may be detected, which may be more obvious at the border of the tapetum. 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 (see Figures 6 & 7). This can first be seen in the smaller blood vessels. As the disease progresses the head of the optic nerve which can be seen exiting the back of the eye starts to look atrophied.

There are some potential difficulties in making an early diagnosis of PRA. Some breeds of dog, particularly the smaller breeds may have a very much reduced size of tapetum and some dogs have no tapetum. This is a perfectly normal variation but can make it more difficult to detect the retinal thinning that develops with PRA. In other dogs the tapetum may be a more gray color and less reflective than in dogs with a bright yellow tapetum. This normal variation can also make the early detection of retinal thinning more challenging.

The size and extent of retinal blood vessels is another feature that can vary quite a lot between individual dogs. In general the smaller breeds, such as the Tibetan Terrier, tend to have less prominent blood vessels. As a loss of diameter of retinal blood vessels is one of the features that is looked for in the early detection of PRA in eye examinations, this can complicate early diagnosis. To distinguish between a normal dog that has less prominent retinal blood vessels and a dog with blood vessel thinning due to PRA the ophthalmologist looks for the presence of early retinal thinning. In dogs with PRA retinal blood vessel attenuation will be accompanied by retinal thinning. Some of the normal variations in the dog fundus are shown in Figures 2 to 5.



**Figures 2, 3, 4 & 5.**

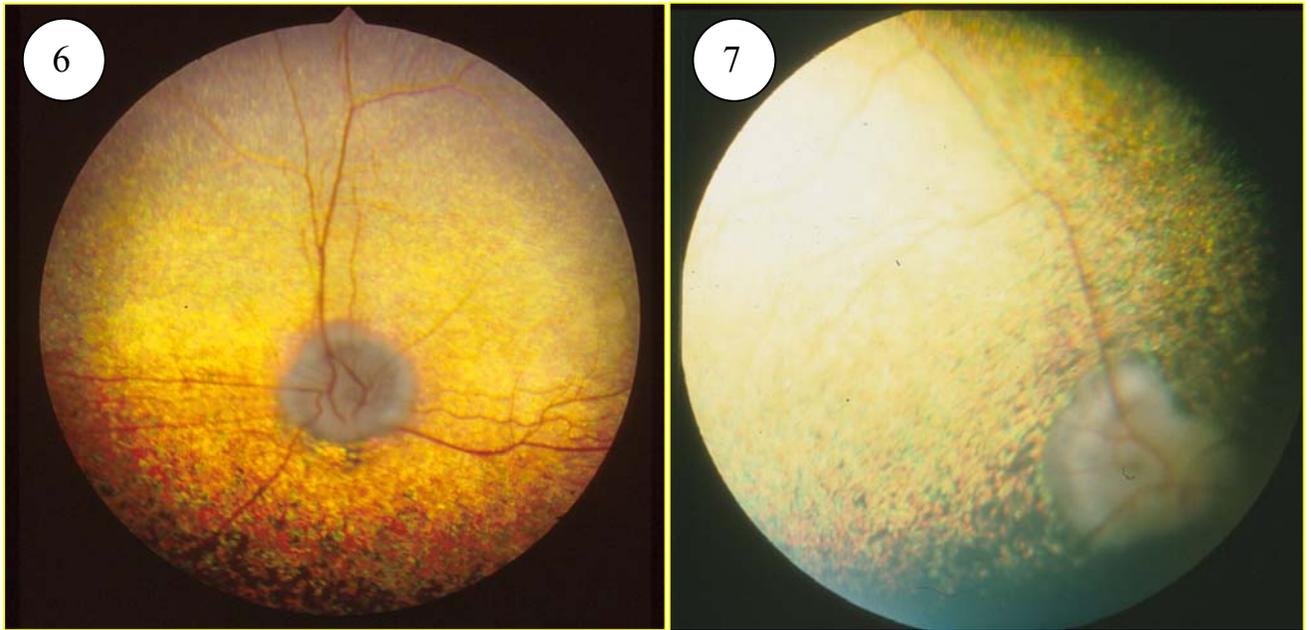
The appearance of the back of the eye (fundus) of four normal dogs showing the variation in normal appearance.

Note the difference in tapetal color.

The extent of the tapetal fundus area is decreased in the eye in figure 5, with the transition to nontapetal fundus occurring above the optic nerve head.

Figures 2 and 3 are examples with more extensive retinal blood vessels while Figures 4 and 5 have less extensive blood vessels. This is normal variation rather than being a feature of disease.

There is also quite a range of appearances of the optic nerve head, with the optic nerve head in Figure 3 looking more prominent than the others.



**Figures 6 and 7.**

These are examples of dogs with PRA. There is increased reflection from the tapetal fundus. The intensity of the camera flash had to be reduced to prevent over exposure of the pictures. Quite advanced retinal blood vessel attenuation has also developed in both instances and the optic nerve heads are showing some signs of atrophy.

### **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 types of ERG protocol. ERGs are commonly used by veterinary ophthalmologists to check that the retina is functioning before removing a cataract, or to investigate a dog that has suddenly gone blind and may be performed in a conscious or sedated dog. This sort of ERG would detect PRA

relatively late in the disease process where there is already advanced retinal degeneration that can be detected by examining the eye with the ophthalmoscope. For early detection of PRA a more detailed ERG needs to be performed. This requires that the dog is anesthetized and a quite extensive protocol is usually performed. It is essential that the normal range of results that can be expected from a breed is known because the response does vary between different breeds. Also the response varies with age; the ERG responses mature by about seven weeks of age and then decrease in magnitude slightly as the dog becomes a young adult. As dogs then become older the response gradually decrease as a normal part of aging

## **Research in to PRA in Tibetan Terriers**

The studies being performed at Michigan State University into PRA in the Tibetan terrier is funded by the American Kennel Club Canine Health Foundation and the Tibetan Terrier Club of America. The approach is to investigate potential candidate genes that could cause PRA and see if they are responsible for PRA in the breed.

## **The Future**

Once the PRA causing gene mutation is discovered it will be possible to develop a DNA-base test that can be performed on a small blood sample or even a cheek brushing. Such a test can tell if a dog is PRA-affected, PRA-carrier or genetically normal. This allows breeders the opportunity to still breed from PRA-carrier dogs.

To prevent any affected puppies being produced, if a carrier is used it must be mated with a genetically normal dog. This allows breeders to continue to use carriers that have some other features that are worth preserving within the breed. This also means that the available gene pool is not restricted. This is important as in the desire to very rapidly get rid of an undesirable feature (e.g. PRA) limiting the dogs used for breeding may result in the emergence of a different genetic problem, for which there is no genetic test.

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