



## Progressive Retinal Atrophy in the Irish Setter

**Progressive Retinal Atrophy (PRA)** is a well-recognised inherited condition that many breeds of dog are predisposed to. The condition is characterised by bilateral degeneration of the retina which causes progressive vision loss that culminates in total blindness. There is no treatment for PRA, of which several genetically distinct forms are recognised, each caused by a different mutation in a specific gene. The various forms of PRA are typically breed-specific, with clinically affected dogs of the same breed usually sharing an identical mutation. Clinically affected dogs of different breeds, however, usually have different mutations, although PRA-mutations can be shared by several breeds.

A mutation for an early-onset form of PRA, known as *rcd1*, was identified in Irish Setters as long ago as 1993, and is well-documented to affect dogs from a few weeks of age. More recently dogs have been identified with a seemingly different form of PRA that affects dogs later in their lives and is known to be different from *rcd1*. This alternative form became known as "LOPRA" – for Late-Onset PRA. Unlike *rcd1*, where all dogs became affected at almost exactly the same age the age of onset of dogs with LOPRA varied, from a few years of age (2-3 yo) up to old age (10-11 yo). It was unclear whether these dogs all shared the same form of PRA or whether there were genetically distinct forms of PRA segregating in this breed.

### Mutation Identified

In 2011 geneticists working in the Kennel Club Genetics Centre at the Animal Health Trust identified a recessive mutation that is associated with the development of LOPRA in the **Gordon Setter**. Owners of Gordon Setters with LOPRA report that their affected dogs develop night blindness in the first instance, which is indicative of a rod-cone degeneration, so we have termed this mutation *rcd4* (for rod-cone degeneration 4) to distinguish it from other, previously described, forms of rod-cone degeneration.

Following our work with *rcd4* in the Gordon Setter we have found some Irish Setters that have been diagnosed with PRA also carry two copies of the *rcd4* mutation. As a result the AHT will make the *rcd4* DNA test available to Irish Setters, from **August 1<sup>st</sup> 2011**. The DNA test we are offering examines the DNA from each dog being tested for the presence or absence of this precise mutation and is thus a 'mutation-based test' and not a 'linkage-based test'.

### Other Forms of PRA

The research we have carried out to identify the *rcd4* mutation has revealed that there are at least three forms of PRA segregating in the Irish Setter; *rcd1*, *rcd4* and an additional, third form, that has yet to be identified.

We know there is a third form of PRA because of the ten dogs with LOPRA, whose DNA we have been sent to analyse, only 7 have two copies of the rcd4 mutation. The remaining 3 dogs do not carry either the rcd1 or rcd4 mutations, meaning their PRA must be due to another, as yet unidentified, mutation. There is some evidence that this third form of PRA has, on average, an earlier age of onset than rcd4, but we need to examine more dogs before we can confirm this.

The age at which dogs with the rcd4 mutation develop PRA seems to vary and we know about dogs as young as 4yo and as old as 10yo, that have been diagnosed with LOPRA, and that carry two copies of rcd4 mutation. But it is important to remember that the age at which a dog is diagnosed with PRA can vary according to circumstances, and is not necessarily the same age at which it started to develop PRA. For example, a dog whose PRA is detected at a routine eye examination will have an earlier age of diagnosis than a dog whose PRA was only detected once it started to lose its sight. It is also possible that the dogs that have developed PRA very early also carry the mutation for the third, unidentified, form of PRA (as well as rcd4) and it is this 'mid onset' mutation that has caused them to develop PRA at a relatively young age. More research will be required to understand the variability in age of onset more fully.

Our research indicates **rcd4** is a common form of PRA among Irish Setters and the development of this test therefore enables breeders to slowly decrease the frequency of an important form of PRA in their lines. However, because we know that at least one other form of LOPRA exists within the breed, we cannot guarantee that any dog will not develop PRA, even if they are clear of the rcd4 mutation.

### **Rcd4 DNA Test**

Breeders using the rcd4 DNA test will be sent results identifying their dog as belonging to one of three categories. In all cases the terms '*normal*' and '*mutation*' refer to the position in the DNA where the rcd4 mutation is located; it is not possible to learn anything about any other region of DNA from the rcd4 DNA test.

**CLEAR:** these dogs have two normal copies of DNA. Clear dogs will not develop PRA as a result of the rcd4 mutation, although we cannot exclude the possibility they might develop PRA due to other mutations they might carry that are not detected by this test.

**CARRIER:** these dogs have one copy of the mutation and one normal copy of DNA. These dogs will not develop PRA themselves as a result of the rcd4 but they will pass the mutation on to approximately 50% of their offspring. We cannot exclude the possibility that carriers might develop PRA due to other mutations they might carry that are not detected by this test.

**GENETICALLY AFFECTED:** these dogs have two copies of the rcd4 mutation and will almost certainly develop PRA during their lifetime. The average age of diagnosis for dogs with rcd4 is 10 yo, although there is considerable variation within the breed.

### **Advice**

Our research has demonstrated that the frequency of the rcd4 mutation in Irish Setters is high and approximately 30-40% of dogs might be carriers. The mutation is recessive which means that all dogs can be bred from safely but carriers and genetically affected dogs should only be bred to DNA tested, clear dogs. About half the puppies from any litter that has a carrier parent will themselves be carriers and any dogs from such litters that will be used for breeding should themselves be DNA tested prior to breeding so appropriate mates can be selected. All puppies that have a genetically affected parent will be carriers.

It is advisable for all breeding dogs to have their eyes clinically examined by a veterinary ophthalmologist prior to breeding and throughout their lives so that any cases of PRA caused by additional mutations can be detected and that newly emerging conditions can be identified.