**Late-Onset Progressive Retinal Atrophy in the Gordon Setter**

A mutation responsible for the development of Progressive Retinal Atrophy (PRA) in the Gordon Setter has been identified by geneticists working in the Kennel Club Genetics Centre at the Animal Health Trust.

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.

Owners 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.

The mutation is recessive and 19 out of the 21 Gordon Setters in our study that had clinical signs of PRA were homozygous (carried two copies) for this mutation, indicating it is the major cause of PRA in the breed. Two dogs in our study had PRA but did not carry the *rcd4* mutation, indicating there might be another, genetically distinct, rarer form of PRA segregating in this breed.

The research that led to identification of the *rcd4* mutation was funded by many different organisations, including the Kennel Club Charitable Trust, the British Gordon Setter Club, the Gordon Setter Field Trial Society, the Gordon Setter Association, the Gordon Setter Club of Scotland and the LUPA project (www.eurolupa.org.uk) as well as several individuals who have also contributed significantly. The AHT would like to thank sincerely all the organisations and individuals who donated funds to help support the research as well as all the owners who contributed DNA and information from their dogs.

**Late-Onset 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 “LOPR” – 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 1st 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 be 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.

Late-Onset Progressive Retinal Atrophy in the Tibetan Terrier

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.

Other Forms of PRA in the Tibetan Terrier

We have tested DNA from 17 Tibetan terriers affected with PRA and found 3 of them were homozygous (carried two copies) for the rcd4 mutation. This indicates that there is at least one additional, genetically distinct, form of PRA segregating in the Tibetan terrier, that is caused by an as yet unidentified mutation and that this additional mutation(s) is probably more common than the rcd4 mutation. At the time of writing (September 2012) we are investigating the frequency of the rcd4 mutation in a random subset of Tibetan terriers and expect to be able to update the Tibetan terrier community with the results by the end
of October 2012. It is important for owners to appreciate that the rcd4 DNA test detects the rcd4 mutation only and cannot provide any information regarding the additional, currently unknown PRA mutation(s).

**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**

The rcd4 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.