

Dachshund PRA Update 27/10/07 (Re-issued 08/09/08)

Cone-Rod Dystrophy in Dachshunds and English Springer Spaniels -

A new name for an old disease

The aim of this document is to clarify current nomenclature (classification) for the retinal degeneration that affects miniature longhaired (MLHDs), miniature smooth haired (MSHDs) Dachshunds and English Springer Spaniels (ESSs).

It was first documented in the MLHD, and was called Progressive Retinal Atrophy (PRA). PRA is the collective term for a group of inherited eye diseases, of which there are several different, breed-specific forms that are due to mutations in different genes. In most forms of PRA the rod photoreceptors in the retina (which are responsible for vision in low light conditions) degenerate before the cone photoreceptors (which work best in mid to high levels of light and have the ability to detect colour). Hence poor night vision, or night blindness, is often the first indication that a dog has PRA. All forms of PRA studied to date result in blindness, but at different ages from a few months to several years.

Work undertaken at the Animal Health Trust identified the genetic mutation described in the MLHD and a DNA test was made available to MLHDs in February 2005. The identical mutation has since been found to be present in the MSHD population, and also in the English Springer Spaniel (ESS) and now the same test is offered to those breeds also.

In parallel to the genetic studies, work carried out by scientists at the Institute of Ophthalmology, London, in collaboration with the AHT and published in September 2007, revealed the disease the MLHDs suffer from is in fact a cone-rod dystrophy. In other words the cones degenerate before the rods. The disease has been termed cord1, for cone-rod degeneration. The MSHDs and ESSs share the identical mutation to the MLHDs and therefore also suffer from this cone-rod dystrophy.

To date, few canine cone-rod dystrophies have been studied in depth, although a very similar condition in the Wire-Haired Dachshund has been described in Norway. However, work with human cone-rod dystrophy patients has indicated that the condition can have a very late age of onset, and the levels of visual impairment can be variable between patients - similar to our findings for the progression of cone-rod dystrophy in miniature dachshunds.

We do know that the cord1 mutation can lead to blindness in MLHDs, MSHDs and ESSs. It is also eminently possible that dogs that are genetically affected, but that retain vision into later life, can produce offspring that develop clinical signs and go blind at an early age. We must stress that the testing of breeding stock for this cord1 mutation should be a priority and also that matings between two carriers should be avoided.

In summary, MLHDs, MSHDs and ESSs are affected by a cone-rod dystrophy, known as cord1, which was originally referred to as PRA. The DNA test offered by the Animal Health Trust tests for the mutation that causes this disease; the mutation is identical in MLHDs, MSHDs and ESSs. If your dog's DNA has been tested for PRA at the AHT it would have been for the cord 1 mutation - you DO NOT need to have your dog re-tested.

Dr Cathryn Mellersh
Animal Health Trust

From: Dr. Cathryn Mellersh

AHT 03/09/08

Much of what we have been doing has been directed at mini longs, just because that is the variety that we have most data for, but we expect our findings to apply to all varieties.

The PhD student that I jointly supervise with David Sargan at Cambridge University has been doing 'functional' studies to try and understand how the mutation we have identified, and that forms the basis of the test we run, actually causes PRA. The experiments she has been doing are very complex, and still very much ongoing, so it's a bit too early to summarise what she has found- but suffice to say we are very actively investigating this aspect. We hope that by understanding how the mutation causes cone-rod dystrophy we will better understand the variation.

Claudia Busse, an ophthalmologist at the AHT has travelled the length and breadth of the UK examining mini longs that carry two copies of the mutation. She took with her a portable ERG machine, that measures the electrical impulses within the eye and thus obtains a more sensitive measure of how the eye is functioning than an ophthalmological examination alone can obtain. She has made some very interesting findings- although all the dogs she examined appeared to have normal eyes it seems their ERG signals were reduced - in other words their cones were not functioning normally at all. This is very preliminary data, and has yet to be formally confirmed, but if it is true it indicates that all those dogs that seem to have normal eyes may well in fact have 'faulty' eyes.

A research group in Norway has identified a different mutation, in a different gene, that causes PRA in standard wirehired dachshunds. In collaboration with this group we have tested many dachshund samples to see if any carried this additional mutation that could explain the variation we see in age of onset, rate of progression etc. None of the samples we sent him carried the mutation, meaning we can exclude this gene/mutation as the source of variation.

From: Bryan McLaughlin

AHT 12/09/08

Attached is a list of Mini-smooths and Mini-wires that have been submitted for research.

There are 123 MSHDs, of which 67 were genotyped. i.e. checked for the Cord1 mutation. 21 of these had 2 copies of the mutation - genetically affected. 22 had 1 copy - genetic carriers. The remaining 24 were clear and therefore genetically normal.

Clinically the MSHDs sample pool had 7 PRA affected, 2 with clear eye exams (although mostly not ERG tested), the remaining 84 were of unknown status. 6 of the 7 affected individuals are homozygous (2 copies) for the Cord1 mutation, and the other had a dubious diagnosis as it also suffered from severe cataracts but displayed ERG charges indicative of PRA. Incidentally this dog had one copy of the mutation. i.e. a carrier.

There are also 51 MWHDs, of which 18 were genotyped. 3 of these dogs are clinically PRA affected but all clear of the Cord1 mutation. These were non-UK samples, two from a breeder in New Zealand, and one came from a lab in Finland. A single individual possessed one copy of this mutation. Further work is being carried out by a lab in Finland, we have shared some of our samples anonymously and they are looking into the possibility of another mutation in another gene that interacts with the protein product encoded in Cord1.

As a diagnostic test, things have been going really well. There have been 660 mini-smooths submitted for testing, half of which had arrived before the launch of the test this year at Crufts. Of these, 125 are genetically affected (2 copies), 295 carriers (1 copy), 209 clear, and the remaining 31 are yet to be processed.

This is all very good I believe, but the only thing I cannot comment on is the clinical status of these dogs as that information isn't provided or requested.

**Retinal degeneration in the Miniature Long-haired & Miniature Smooth-haired
Dachshund
Dr. Jeff Sampson KC/AHT
04/12/07**

The demands on responsible dog breeders grow ever greater, but it is imperative that we all stay focused in order to maximise the chances that the puppies we breed will live a long, happy and healthy life, giving their owners the best possible dog owning experience. One of these responsibilities is to screen potential breeding stock with any breed-specific health screening tests that are available.

One such test has recently become available for the Miniature Long-haired Dachshund, as well as the Miniature Smooth-haired Dachshund, a DNA test for the mutation, known as cord-1 that can cause retinal degeneration and blindness. There has been some debate over the precise clinical description and name of this condition, and recent DNA test results suggest that there is a far greater spread of ages at which genetically affected dogs begin to show clinical signs. However, the cord-1 mutation can and will cause blindness in the breed.

Many of the dogs homozygous for the cord-1 mutation, dogs that are genetically affected, show early clinical signs, which is the classic clinical description of this condition in the breed, but others have reached old age without showing clinical signs. However, the effect of the mutation in a parent will not necessary predict how the disease, if inherited, will progress in one of its offspring. It is therefore imperative that breeders put aside the debate about the condition's clinical name and expression, as interesting as it is, and concentrate on using the DNA test that is available to begin to reduce the prevalence of the cord-1 mutation in the breed.

The first important step is for breeders to DNA test all potential breeding stock before they are used to produce future litters. This will inform the breeder as to a dog's genotype, whether it is a clear/normal dog (two copies of the normal gene), a carrier (one copy of the normal gene and one copy of the mutant, cord-1, gene) or an affected (two copies of the cord-1 mutation), and allow them to use this information when selecting a genetically compatible mate.

Obviously, if a dog comes back as clear/normal, it doesn't pose an issue with respect to potential retinal degeneration because it can only pass normal gene copies onto its offspring. If a dog is DNA tested as a carrier, then this will need to be taken into consideration by the breeder selecting a mate for the dog. The offspring of a carrier will have a 1 in 2 chance of inheriting the carrier's cord-1, mutant gene. So, a DNA tested carrier should not be mated to an untested dog (because there is no idea about its genetic status), another carrier or an affected dog, because the chances of at least one affected puppy being born will be far too high. However, a carrier can be mated to a DNA-tested clear/normal dog.

If a carrier is mated to a clear/normal dog, then each of the offspring will have a 1 in 2 chance of being clear/normal and a similar chance (1 in 2) of being a carrier. importantly, none will be clinically affected because even carriers are clinically normal. Furthermore, DNA testing the litter will reveal which of the puppies are genetically normal and which are carriers.

The availability of this DNA test will also allow breeders to contemplate breeding from affected dogs, something that would be inconceivable in the absence of a specific DNA test.

If an affected dog is mated to a DNA-tested clear/normal dog, then all of the puppies will be carriers, but none will become clinically affected. One of this carrier first generation could then, in the fullness of time, be mated, again to a DNA-tested normal dog, and the puppies in this second generation will have a 1 in 2 chance of being clear/normal or a carrier.

It is crystal clear that the use of this new DNA test will have immense impact on the prevalence of the cord-1 mutation in the breed. Experience of other, similar DNA tests in other breeds shows us that, if used properly, a DNA test will have an immediate impact on the future occurrence of clinical disease in the breed and, over a number of years of testing, will eventually reduce the frequency of the mutation to the point of irrelevance for the breed. However, as important as DNA testing for cord-1 is, breeders should not lose sight of their primary objective in breeding, to produce dogs of the correct type and temperament. DNA testing should be used to give breeders confidence that when they have selected appropriate parents none of the subsequent litter will become clinically affected.

So, no one should really be breeding from a dog unless they feel that it is likely to produce good breed examples. When choosing that clear mate for your carrier dog, choose a dog that you would have liked to use anyway, who happens to be clear of the cord-9 mutation. Finally, when you choose that clear bitch from a carrier clear/cross, choose her because she is a good specimen, not simply because she is a clear. Take your time and be patient. Avoid matings that are likely to produce clinically affected dogs and be sure that when you do choose a clear dog to breed on from it is a good specimen of the breed.