



Canine Genetics Progress Report

Breed: Golden Retriever

Condition: Hereditary cataract (HC) and Progressive Retinal Atrophy (PRA)

Date: 01/02/2010

Recent / Current Funding:

Funding Body: Kennel Club Charitable Trust

Amount: £250,000

Start Date: 01.03.2005, duration 36 months

This grant has now expired.

The AHT staff that are currently investigating PRA and HC in the Golden retriever are generously supported by the Kennel Club, as part of the Kennel Club Genetics Centre at the Animal Health Trust, but resources such as consumables and laboratory materials are being currently funded solely by donations from funding organisations, breed clubs and individuals.

The AHT is very happy to report it is now collaborating with scientists from the Swedish University of Agricultural Sciences on the PRA project. Cathryn Mellersh and her PhD student, Louise Downs, recently travelled to Uppsala, Sweden, to discuss the results obtained to date and also how the two teams could work together to progress the project with maximum efficiency and momentum.

Brief Summary Of Project

As we have reported previously, this project aims to compare the DNA from dogs affected with either PRA or HC with DNA from unaffected dogs, in order to identify regions of the genome that are consistently shared between dogs affected with each condition, but not with unaffected dogs. Once regions associated with either condition have been identified we carry out additional experiments to ‘magnify’ the regions identified initially, to hopefully refine the region of interest for each condition. This stage of the project is known as ‘fine-mapping’. When we have refined the region as much as possible we will sequence candidate genes within the region to find the actual mutation responsible for each condition and develop DNA tests that we will offer to breeders.

PRA progress

In a previous report we announced **that we have identified a region of the genome that is associated with PRA in the Golden retriever**. This means we are almost certain we know the stretch of DNA that harbours a mutation that causes PRA in this breed. We can now recognise the region of chromosome that carries the PRA mutation and tell it apart from versions of the same chromosome that don’t carry the mutation. To put these advances into context, the genome of the dog consists of 2,500,000,000 nucleotides of DNA. If each nucleotide measured 1mm the canine genome would stretch 2,500 km or 1600 miles. For UK readers, this is from Lands End to John O’Groats and back again. We have now successfully refined the region of DNA that contains the PRA mutation to the equivalent of just 1 km, or 0.04% of the total genome. As expected, nearly all the dogs affected with PRA carry two copies of this ‘PRA’ chromosome and it is noteworthy that we have identified Golden retrievers from both the UK and Scandinavia that carry two copies of the PRA chromosome.

Since the last report we have been studying the genes that lie within this PRA region, and have identified one gene that is a very strong candidate for causing PRA. Our initial investigations with this gene are very promising. There are several important investigations that still need to be done but we hope that if our studies go according to plan it is likely we will be able to offer a DNA test for PRA in Golden retrievers within the next 12 months.

Interestingly, however, some dogs with clinical PRA do not carry two copies of the ‘PRA chromosome’ described above, suggesting there is also another form of PRA in the breed. It is worth noting that all the samples we are working with have been genotyped for the *prcd* mutation, to exclude the possibility that the dogs are affected with the *prcd* form of PRA. Since our last report we have analysed DNA from several additional PRA cases collected by Tomas Bergstrom’s team (Sweden) and our initial observations have been upheld; the majority of Golden retrievers affected with PRA carry two copies of the PRA region we have identified but a small minority carry different versions of this chromosome. We have some very initial evidence that these other PRA cases may have share another region of the genome, but this remains to be verified.

HC

In a previous report we announced that we had identified a region of the genome that seemed to be associated with HC in the Golden retriever. Since the last report we have undertaken a Whole Genome Scan (WGS) with additional HC samples, in an effort to confirm the HC region. The new data has been added to the data collected previously, and the combined dataset has been carefully analysed, using several different methods. We have also combined the Golden retriever data with data from other breeds affected with HC, to see if we can identify any regions of the genome that are shared between HC breeds. Our combined analysis has included data from up to 41 Golden retrievers affected with HC and 75 dogs with clear eyes.

After all the above analysis there is still one region of the genome that we believe might be associated with HC in the Golden retriever. However, the evidence to support this region is not as strong as the evidence to support the PRA region, so whereas we would describe ourselves as ‘*virtually certain*’ we have found a region containing a PRA mutation we would only describe ourselves as ‘*reasonably certain*’ we have found an HC region. The fact we have analysed the DNA from a significant number of affected dogs but can still only be reasonably certain about the HC region means that the condition is almost certainly the result of more than one mutation and possibly several mutations are involved. This conclusion is supported by our findings in other breeds as well, all of which suggest there are multiple genes associated with HC.

We will continue to analyse DNA from HC affected dogs and older dogs with clear eyes, until we get to a point where we can either confirm or exclude our initial HC region, and/or identify additional regions associated with HC that we can investigate further. We have analysed the DNA from all of the HC affected dogs that we currently have samples from, **so we have a real need for samples from more dogs with HC. We also need samples from older dogs whose eyes are still clear (as confirmed by an ophthalmologist).**

MRD

MRD is not currently being actively worked on at the AHT, due to a need for additional samples from affected dogs and additional funding.

Sample Collections

The pace at which GR samples have been submitted to the AHT has increased significantly in recent years. During 2007 samples from only 12 Golden retrievers were submitted to the AHT, whereas in 2008 the number increased to 58, and 156 samples were submitted during 2009.

The Animal Health Trust would like to thank all Golden retriever owners and breeders who have submitted samples and information from their dogs. The DNA technology available with which to identify mutations is now exceptionally sophisticated but nevertheless is of little use without DNA from appropriate dogs. **Although we are making very good progress with both these diseases we would still encourage owners of affected dogs to consider donating samples from their dogs.**

The DNA can be submitted as 5ml blood samples preserved in EDTA (to only be collected from UK dogs at the same time blood is being drawn for another purpose) or as cheek swabs. Swab kits and full instructions can be obtained from the AHT by contacting Bryan McLaughlin (bryan.mclaughlin@aht.org.uk) or Lisa Jeffery (lisa.jeffery@aht.org.uk)

A copy of an eye certificate confirming HC / PRA diagnosis and a 5-generation pedigree must accompany each sample. Full details of all information that is required is included in each swab kit.

Anybody who is unsure whether or not their dog(s) could usefully contribute to our HC and PRA studies should feel free to contact either Bryan McLaughlin (bryan.mclaughlin@aht.org.uk) or Cathryn Mellersh (cathryn.mellersh@aht.org.uk) for more information.

Once the research is complete and DNA tests have been developed the AHT will provide the owners of all dogs that were used in the research with their DNA test results free of charge, upon request. All personal and health information is treated with the utmost confidence.

It is very important that owners do remember to keep the AHT updated if the health status of their dog changes after they have submitted a DNA sample. If, for example, a dog was clear when its DNA was sampled and sent to the AHT, but it unfortunately goes on to develop HC at a later date it is very important the AHT is informed.