Progressive Retinal Atrophy (PRA) in the Lhasa Apso

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Talk plan

- PRA
- PRA in the Lhasa Apso
- Our study
- DNA test and breeding advice

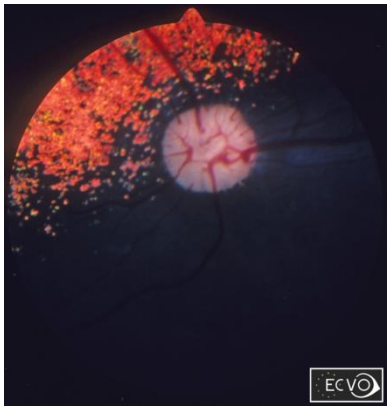
What is PRA?

- Progressive Retinal Atrophy
- Retinal degeneration
- Collective term
- Rods and cones

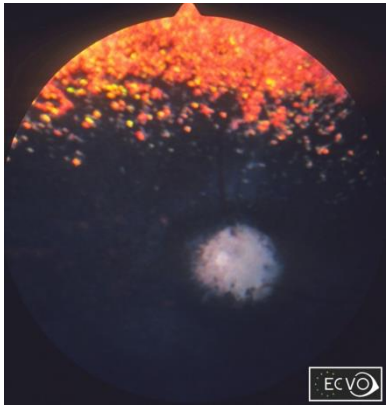
- Blindness
- >100 breeds
- ~28 mutations previously identified
- Genetically heterogeneous

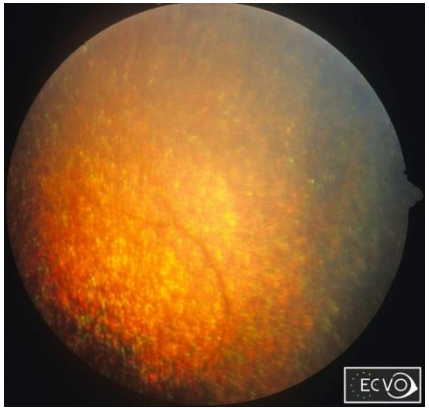
Clinical signs of PRA

Normal



PRA affected





- Vison is normal from birth and depending on the age of onset, progressively degenerates over time
- Photoreceptor response in the retina depletes which leads to a loss of vision
- Typically loss of night vision first followed by loss of day vision
- An eye examination by an ophthalmologist will show a change in the blood vessels in the retina (vascular attenuation) and a 'shiny glow' of the reflective layer behind the retina (tapetal hyperreflectivity)

PRA in the Lhasa Apso

- Typically mid age of onset, although difficult to pinpoint the exact age of diagnosis
- Currently on Schedule A of the BVA/KC/ISDS eye scheme
- Autosomal recessive mode of inheritance

Recessive Disease

- PRA has an autosomal recessive mode of inheritance

- This means that a dog has to have two copies of the defective gene (one inherited from each parent) for it to be affected by the disease.

- Individuals with one copy of the defective gene and one copy of the normal gene, called carriers, show no signs of disease but can pass the defective gene onto their offspring.

AHT research - GWAS

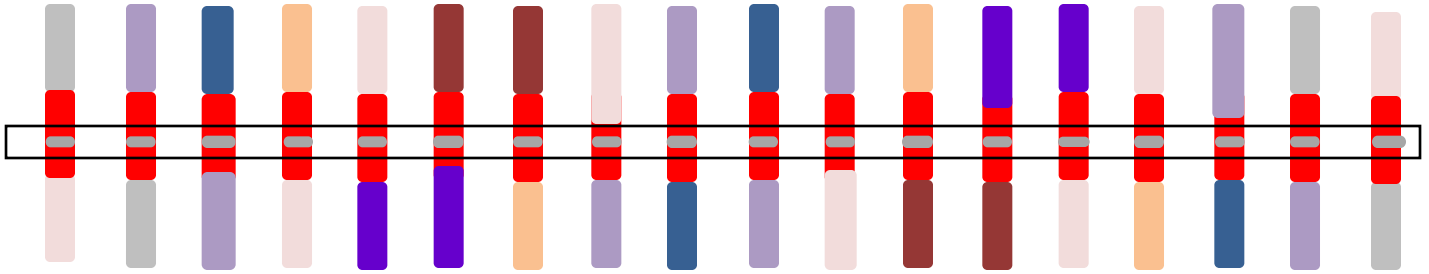
Finding a disease mutation using a Genome Wide Association Study (GWAS)…

- Scans markers across the genome in a set of individuals affected with a particular disease (**cases**) and individuals clear of the disease (**controls**)
- Identifies **a region** associated with a particular disease

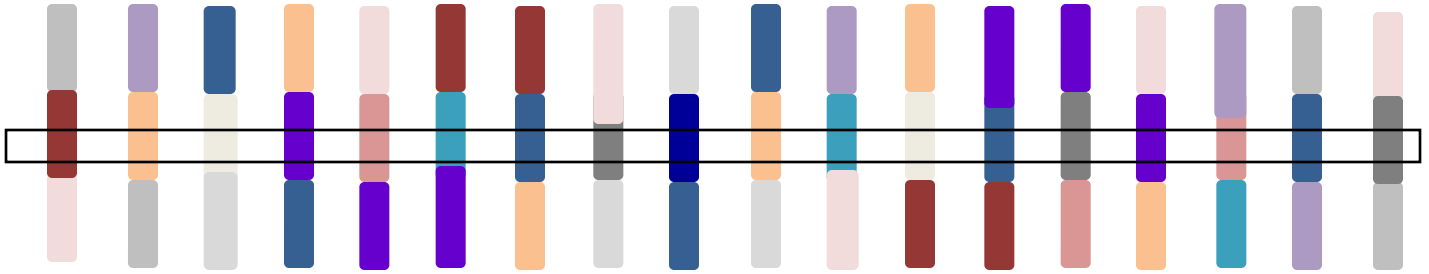
Our study…
17 Lhasa Apso's with PRA (cases)
27 Lhasa Apso's >8 years free of PRA (controls)

Mutation Identification

Affected



Unaffected



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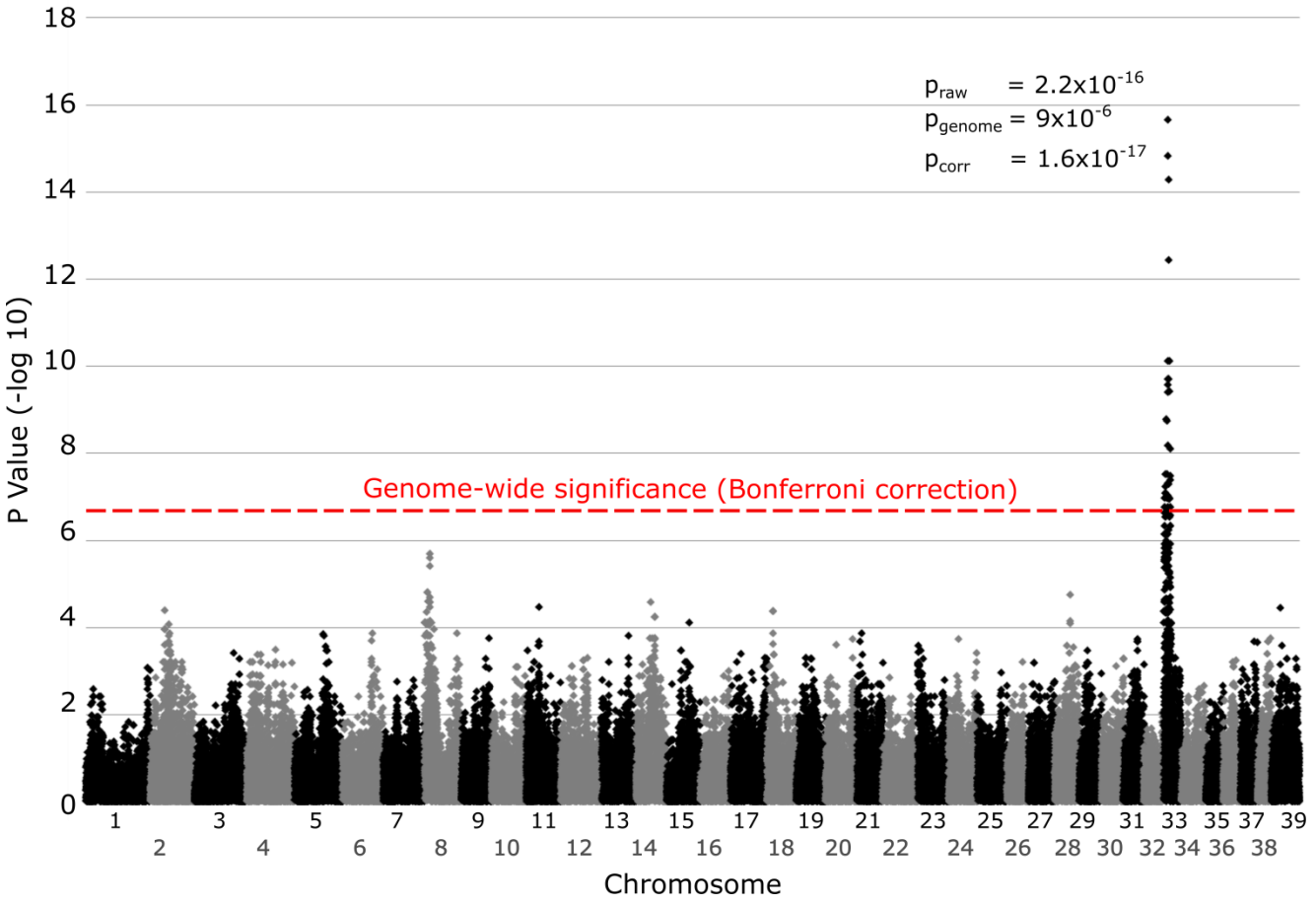
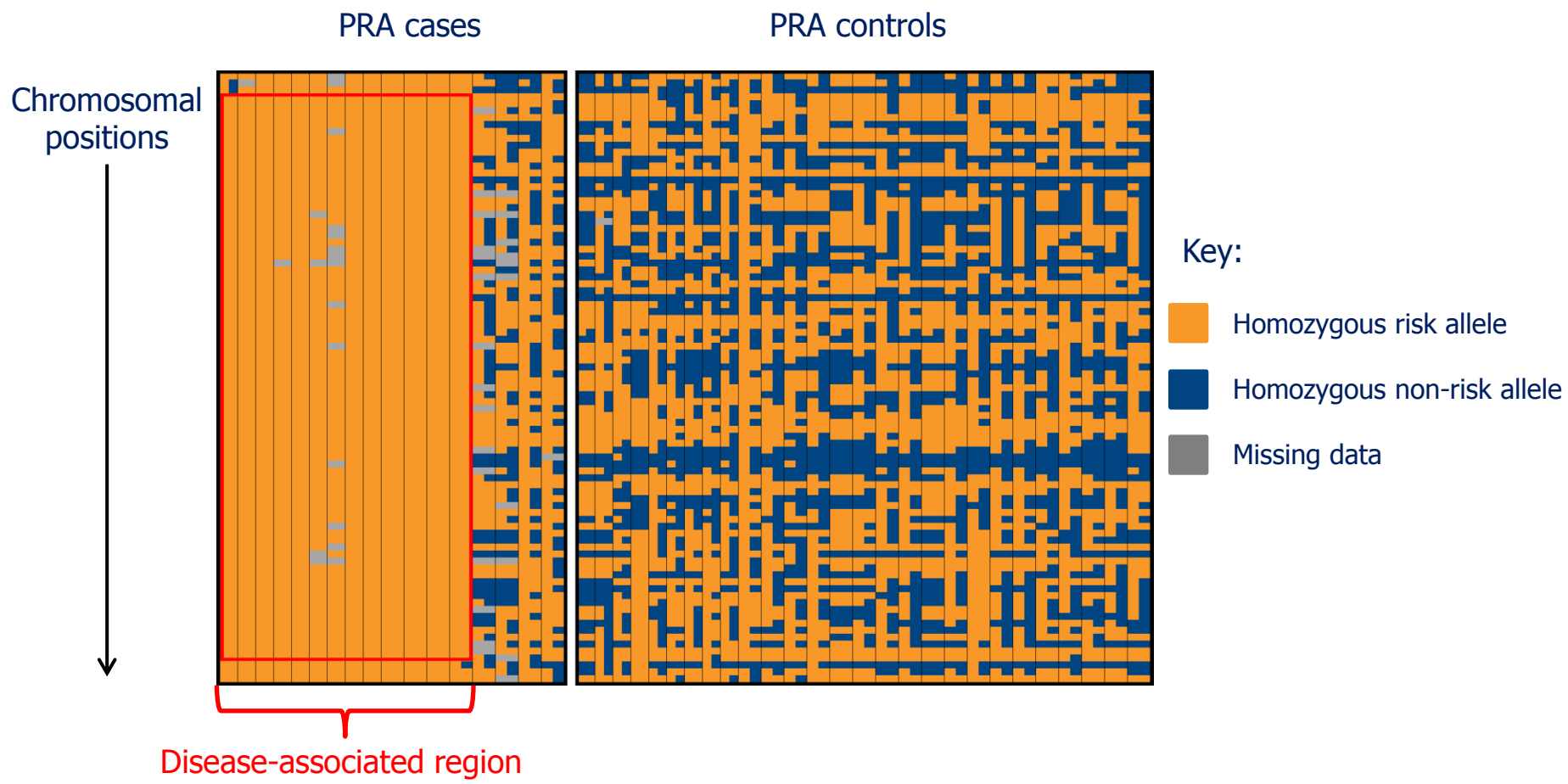
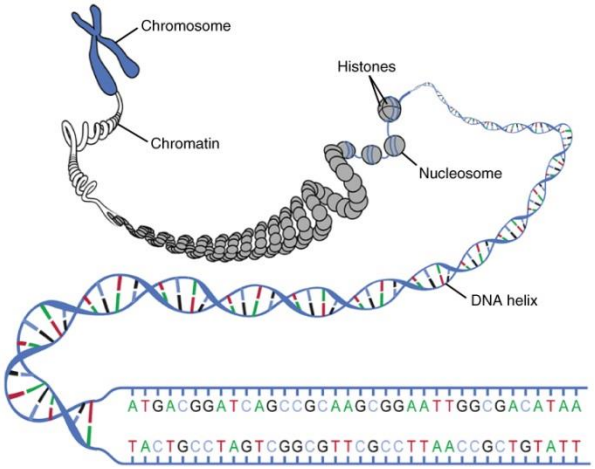


AHT research - GWAS



AHT research - WGS

- Whole genome sequencing (WGS) performed
  - Read the entire sequence of the dog's genome
  - Canine genome = 2.4 billion base pairs



If 1 base pair = 1 letter, this would read the entire Harry Potter series **367 times!**

AHT research

a) GWAS identified **a region** where the mutation lies

- Narrowed down our search from the whole DNA sequence (i.e. 100% of the genome), to just 0.05% of the genome.

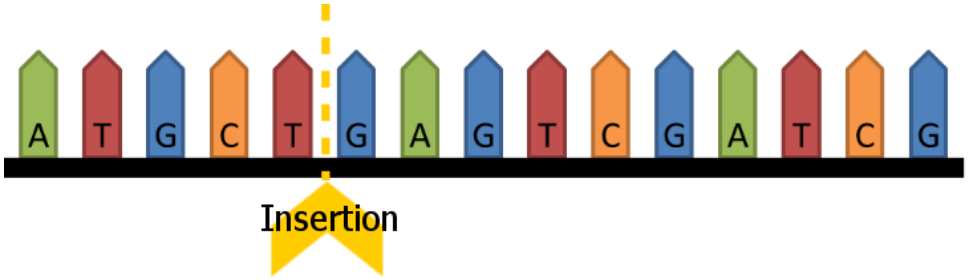
b) WGS enabled us to **zoom** into this 0.05%

- Identified exactly what is causing PRA in these dogs at the DNA level.

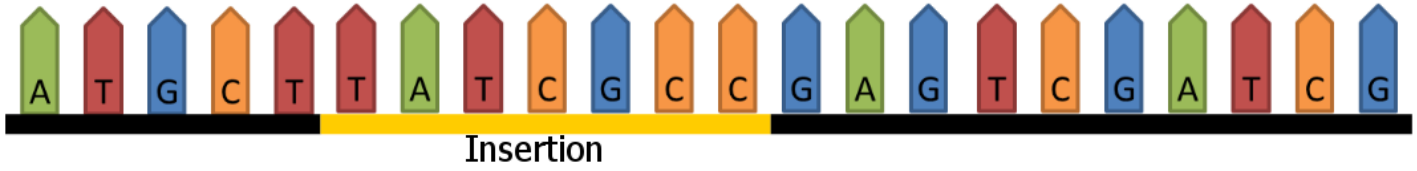
PRA4 mutation

- A large insertion in the normal DNA sequence causes PRA in the Lhasa Apso
- This type of PRA in the breed will be termed 'Progressive Retinal Atrophy - Type 4' or 'PRA4'

Normal DNA sequence



'Mutant' DNA sequence with additional DNA inserted



DNA test developed based on this mutation – official launch date Monday 4th September 2017

DNA test results

There are 3 possible DNA test results:

- **AFFECTED:** The dog has two copies of the PRA4 mutation and is affected or will become affected with PRA.
- **CARRIER:** The dog has one copy of the normal gene and one copy of the mutant gene that causes PRA4. It will not develop PRA but will pass on the PRA4 gene to 50% (on average) of its offspring.
- **CLEAR:** The dog has two copies of the normal gene and will neither develop PRA, nor pass a copy of the PRA4 gene to any of its offspring.

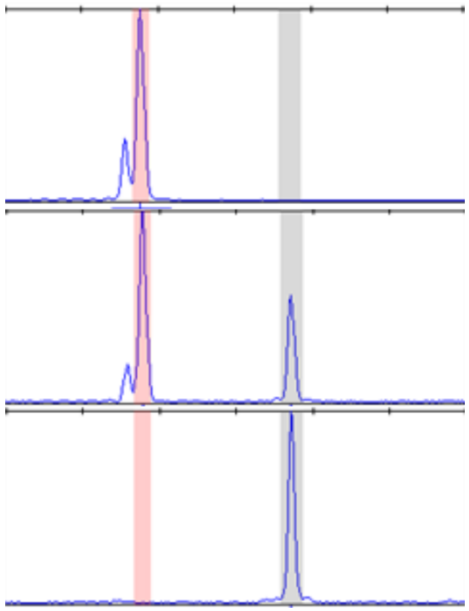
DNA Test

- DNA test looks directly at the DNA sequence to distinguish between the normal allele and affected allele

PRA Affected

PRA Carrier

PRA Clear



Breeding with carriers

- Although we are unsure of the frequency of the PRA4 mutation in the Lhasa Apso breed, this will be monitored now the test is available and updates given to the Breed Club once we have tested more dogs.

- Our advice is to **breed with carriers** for the first few generations following the development of the DNA test

- If carriers are not bred from there could be a rapid reduction of the breed gene pool

Breeding with carriers

- **Remember** – the PRA4 mutation is probably **NOT** the only mutation a dog is carrying
- Carriers can be safely bred with, providing they are mated to a DNA tested dog that is **CLEAR**
- Any puppies that will be bred from need to be DNA tested themselves prior to breeding
- **Non-breeding** pet dogs **DO NOT** need to be DNA tested

Priorities

1. Avoid breeding dogs that could develop PRA
    - PRA is a blinding disease and now there is a DNA test there is **NO excuse** for producing affected dogs

2. Reduce the frequency of the mutation within the breed
    - This can be done slowly, over several generations
    - Allow yourselves time to capture all the other desirable features that are important (e.g. temperament) before restricting breeding to clear dogs only

Combination of Dogs	Outcome	Possibility of puppies with PRA?
Clear X Clear	All puppies will be clear	No
Clear X Carrier	~ 50% of puppies will be clear ~ 50% of puppies will be carriers	No
Clear x Affected	All puppies will be carriers	No
Carrier x Carrier	~ 25% of puppies will be clear ~ 25% of puppies will be affected ~ 50% of puppies will be carriers	Yes
Carrier x Affected	~ 50% of puppies will be affected ~ 50% of puppies will be carriers	Yes
Affected x Affected	All puppies will be affected	Yes

Which dogs qualify for free DNA test results?

Samples submitted to the research study that were either:

a) Lhasa Apso's diagnosed with PRA by a BVA/KC/ISDS panellist (or the European equivalent) with an examination certificate or a referral letter from a veterinary ophthalmologist

a) Lhasa Apso's over the age of 8 years diagnosed as PRA-free by a BVA/KC/ISDS panellist (or the European equivalent) with an examination certificate or a referral letter from a veterinary ophthalmologist

Those eligible to receive free DNA test results will not need to purchase a test and will receive their dog(s) results to the email address provided at sample submission, if the owner so wishes to receive this result.

www.ahtdnatesting.co.uk

Thank you!

- Pauline Torrance; Breed Health Coordinator
- Lhasa Apso Breed Council
- Kennel Club Charitable Trust
- All owners who have contributed samples towards the research
- John Goodyear BVMS CertVOphthal MRCVS

THE KENNEL CLUB GENETICS CENTRE AT THE ANIMAL HEALTH TRUST

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