



Animal *Health* Trust



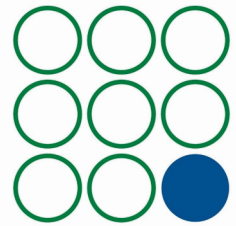
**THE KENNEL CLUB**

*Making a difference for dogs*

**THE KENNEL CLUB**

GENETICS CENTRE

**AT THE ANIMAL HEALTH TRUST**



# Mid-term report

March 2009 - August 2011



## Introduction

Inherited disease within purebred dogs has become headline news in recent years. Strong selection for desired characteristics and the fact that individual breeds are genetically isolated mean that many breeds of dog have reduced gene pools and lower levels of genetic diversity than their cross bred cousins. An unfortunate consequence of this can be the rapid increase of harmful or damaging disease-associated mutations. Inherited conditions observed in some breeds can obviously lead to substantial welfare concerns and, as there are believed to be more than five million purebred dogs in the UK alone, the issue of inherited disease justifies close attention.

The Animal Health Trust (AHT), with support from the Kennel Club Charitable Trust and other funding organisations, has been investigating the genetic basis of canine inherited disease for nearly 20 years. Over the last decade huge advances have been made in the field of canine genetics. These advances started with the development of a comprehensive map of the canine genome and culminated in the sequencing of the entire genome in 2004. Since then high density whole-genome marker arrays have been developed enabling scientists to locate and pinpoint genetic mutations much more easily and quickly than was previously possible, thus enabling the efficient and effective development of diagnostic tests which will help future generations of dogs.

In March 2009, the Kennel Club and the AHT collaborated to create the Kennel Club Genetics Centre (KCGC) at the AHT. The Centre aims to help dog breeders to reduce or eradicate inherited disease from their breeds. This will be achieved by the development of essential tools to minimise the risk of breeding affected puppies and the design of breeding programmes to improve the overall health and welfare of the breed whilst safeguarding the long term genetic health of breeds by preserving genetic diversity.

The KCGC at the AHT is led by Dr Cathryn Mellersh and Dr Sarah Blott, two of the AHT's genetics experts. Both have pioneered screening tests to identify a dog's genetic status and minimise the risk of producing affected puppies.

From March 2009 to December 2013 the KCGC aims to investigate a number of inherited diseases in terms of their heritability, mode of inheritance and prevalence within the breed at risk being studied. Whole Genome Scan technology (WGS) is being performed to identify regions of the genome linked to specific canine inherited diseases. Subsequent fine mapping and next-generation sequencing techniques are being applied to identify the associated mutations leading to the development of genetic screening tests, to determine affected and carrier dogs, which can be performed with simple mouth swabs.

The Centre also aims to introduce new approaches to aid in dog breeding decisions. One major advance is the development of estimated breeding values (EBVs). These will enable whole dog populations to be evaluated for inherited disease – even if individuals haven't been scanned or DNA tested themselves.

In deciding which diseases to investigate, the scientists consider the impact on the health and welfare of dogs, but also the willingness and support of breeders to provide sufficient data and DNA samples for the investigations to be successful.

The KCGC has been established for two and a half years now and this report highlights the progress and achievements made to date.

Since 2009, the KCGC has identified five different mutations that are associated with diseases in 20 breeds of dog. For all of these mutations, the AHT has developed DNA screening tests that determine whether a dog carries zero, one or two copies of the specific mutation being tested for and therefore whether it will develop the condition itself and/or pass the mutation onto its offspring. This information allows owners to make informed breeding decisions that minimise the risk of producing affected dogs. All the tests utilise DNA collected by a simple mouth swab.

Mutations have been identified, and DNA tests developed at the AHT, for:

- 1. Primary lens luxation (PLL) in 17 breeds** (Australian Cattle Dog, Chinese Crested Dog, Jack Russell Terrier, Jagd Terrier, Lancashire Heeler, Miniature Bull Terrier, Parson Russell Terrier, Patterdale Terrier, Rat Terrier, Sealyham Terrier, Tenterfield Terrier, Tibetan Terrier, Toy Fox Terrier, Volpino Italiano, Welsh Terrier, Yorkshire Terrier, Wire-haired Fox Terrier)

PLL is a painful and potentially blinding condition. In PLL affected dogs the fibres which support the lens within the eye break down or disintegrate, causing the lens to become loose within the eye. If the lens moves to the front of the eye rapid onset glaucoma and loss of vision can result.

Since the launch of the DNA test in October 2009, more than 8,750 dogs of 15 breeds, from 40 different countries, have been tested for the PLL mutation. Of these, 327 have been identified as genetically affected and more than 2,800 as carriers.

- 2. Progressive retinal atrophy (PRA) in Golden Retrievers**

Progressive retinal atrophy (PRA) is a well-recognised inherited condition in many breeds of dog. 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 - the most successful way to combat the disease is to identify dogs that carry the mutation and develop informed breeding strategies. The new DNA test has been developed following the identification of the mutation which causes the most common form of PRA among Golden Retrievers in Europe – known as GR\_PRA1. The mutation which causes a second form of PRA is still to be identified.

Since the launch of the DNA test in November 2010, more than 380 Golden Retrievers have been tested, from 16 different countries. Of these, four dogs have been identified as affected and 31 as carriers.

- 3. Late-onset progressive retinal atrophy (PRA) in Gordon Setters**

Gordon Setters suffer from a late onset form of PRA that doesn't typically affect dogs until they are around eight years of age. 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 identified, forms of rod-cone degeneration.

We have identified the mutation for *rcd4*, which we believe is the most common form of PRA in the Gordon Setter, but our investigations indicate that there might be another, genetically distinct, rarer form of PRA in this breed.

Since the launch of the DNA test in March 2011, we have tested more than 950 Gordon Setters from 23 different countries for the *rcd4* mutation. Of these, 119 dogs have been identified as affected and 407 as carriers.

4. **Curly Coat and Dry Eye (CCDE) Syndrome in Cavalier King Charles Spaniels and**
5. **Episodic Falling (EF) in Cavalier King Charles Spaniels (CKCS)**

CCDE, known scientifically as congenital keratoconjunctivitis sicca and ichthyosiform dermatosis, affects a dog's eyes and skin. Affected dogs produce no tears making their eyes incredibly sore. Their skin becomes very flaky and dry, particularly around the foot, and this can make standing and walking difficult and painful. This syndrome appears to be a problem unique to CKCS and most dogs diagnosed with the condition are put to sleep.

Episodic falling is a neurological condition, induced by exercise, excitement or frustration, in which muscle tone increases. During an episode an affected dog is unable to relax its muscles, becomes rigid and often falls over. Affected dogs usually start to demonstrate clinical signs before one year of age, with most cases having their first episode aged four to seven months.

We identified the mutation for EF at the same time as we found the mutation for CCDE (above) and a DNA test has been developed that screens for both mutations simultaneously.

Since the launch of the DNA test in April 2011, we have tested 842 CKCS from 15 different countries for both mutations. Of these, 25 dogs have been identified as affected with EF and more than 230 dogs as carriers of either EF or CCDE.

### **Additional conditions under investigation**

In addition to the success stories outlined above, we are currently investigating many more inherited conditions. We aim to initiate studies on at least five conditions in five breeds each year and launch new DNA tests at the AHT for the majority of conditions under investigation by the end of the five year programme. Since 2009 we have undertaken projects to investigate 10 different conditions in 18 different breeds, and DNA sample collections are underway for many more that will progress to more active investigation once sufficient samples have been collected.

## Estimated Breeding Values (EBVs)

Complex diseases, such as hip dysplasia and epilepsy, are believed to be caused by a combination of genetic and environmental effects. Pedigree information and population-wide data on disease, such as that collected for the BVA/KC health screening schemes, are analysed using advanced statistical techniques to calculate the extent to which a disease is genetic (its heritability) and this information is used to determine EBVs. EBVs are an objective numerical assessment of the genetic status of an individual dog, with environmental effects removed. By using EBVs breeders can distinguish between dogs of high and low genetic risk when selecting parents.

EBVs projects are currently underway for the following conditions:

### 1. Hip and elbow dysplasia

Hip and elbow dysplasia are developmental diseases which affect several breeds of dog, often causing pain, dislocation of the joints and leading to lameness. Data from the BVA/KC hip and elbow dysplasia schemes has been analysed and used to develop EBVs. The Labrador Retriever was the first breed to be analysed and it is expected that EBVs for this breed will become publically available through the Kennel Club Health Finder in early 2012. Several other breeds are currently undergoing analysis and EBVs will also be developed for these breeds.

The introduction of EBVs to more accurately identify genetic risk of hip and elbow dysplasia will:

- allow breeders to plan low risk matings based on parental EBVs
- improve the ability of breeders to select against hip and elbow dysplasia
- result in much quicker progress towards the goal of eradicating these debilitating conditions.

### 2. Syringomyelia and mitral valve disease in Cavalier King Charles Spaniels (CKCS)

Two of the most prevalent diseases in CKCS are syringomyelia, a neurological condition which results in abnormalities of the spinal cord, and mitral valve disease, a heart condition. Examination of pedigree records and clinical scans has shown that both of these conditions have genetic components or are inherited. Our studies have shown significant genetic variation in the risk of developing these two diseases, although other non-genetic factors may also play a role.

EBVs, which will help breeders make more accurate decisions about which dogs to breed in order to minimize the risk of puppies having syringomyelia or mitral valve disease, are currently under development. By using EBVs breeders should be able to more rapidly decrease the occurrence of these diseases in CKCS.

## Population structures and inbreeding

Inbreeding is one of the risk factors for inherited disease in purebred dogs. It is important to understand how the population structure of breeds may be contributing to an increased rate of inbreeding. Analysis of the population structure and rate of inbreeding for all 211 Kennel Club recognised breeds is currently underway.

Kennel Club pedigree records are being used to calculate the rate of inbreeding for each breed over the last 30 years. The rates show how fast inbreeding is accumulating in a breed and indicates the effective population size. This gives a measure of how many individuals are contributing genetically to the population and is a measure of the size of the gene pool in any UK breed.

The analysis also examines how much close inbreeding there is in the breed, and produces other descriptive statistics such as how many dogs are used for breeding and their average number of offspring.

So far we have analysed 38 breeds and published results for the following:

Bearded Collie, Bloodhound, Great Dane, Irish Red and White Setter, Miniature Bull Terrier, Otterhound and Tibetan Terrier.

Generally, our results show that most breeds have an effective population size below the recommended minimum to maintain a sustainably low rate of inbreeding. In many cases there is evidence that inbreeding rates could be much lower, if appropriate breeding strategies were adopted.

Such strategies might include reducing the degree of line breeding used, managing the use of popular sires to reduce their future impact on inbreeding, and using more individuals as sires and dams.

## Mate Select

An online service for dog breeders which is available from the Kennel Club's website has been developed. The program, called Mate Select, is designed to help breeders manage inbreeding and ensure, as far as possible, the good health of the puppies they produce. The service will be available for all breeds.

Breeders simply need the KC registered name, registration number or stud book number of a particular dog, in order to access information on that animal. Mate Select has been designed so that additional tools can be added, as they are developed, and made available to dog breeders.

Phase one of Mate Select, launched in May 2011, enables breeders to:

- access a dog's individual inbreeding coefficient
- access the average inbreeding coefficient for any breed recognised by the KC
- perform hypothetical matings and predict the inbreeding coefficients of the puppies.

We are now creating technologies that will underpin the second and third phases of Mate Select. This includes developing statistical models so EBVs for conditions such as hip and elbow dysplasia can be calculated. We are also researching the impact of 'optimum contributions' (OCs) when applied to dog breeds.

By using OCs we will be able to understand the impact that using any particular dog will have on the future diversity of a breed.

Going forward, once all three tools are operational, we will continue to carry out the routine calculation of EBVs and OCs ensuring the data breeders are accessing is as accurate and up-to-date as possible. We also hope that through our continued research we will be able to develop new features for the program, ensuring that Mate Select remains an innovative and cutting-edge development in dog breeding.

## Summary

The outstanding progress the KCGC at the AHT has made since its launch in March 2009 is already making a significant difference to the health and welfare of many dogs – both individuals and whole breeds.

There is still much to do. We are currently investigating a variety of inherited conditions, including idiopathic epilepsy in Border Collies and hereditary cataract and progressive retinal atrophy in many breeds, including American Cocker Spaniels and Tibetan Spaniels. The results of these investigations will, hopefully, be DNA screening tests that breeders can use to control or even eliminate these debilitating diseases.

We will also continue to advance the tools available to dog breeders, particularly for dealing with the risk of complex diseases. This will include expanding the range of complex diseases for which EBVs are available, and researching new methods for calculating genetic risk. We will also be testing breeding strategies aimed at improving canine health and diminishing the impact of inherited disease using computer modeling. This will enable us to advise breeders on appropriate breeding strategies which are aimed at minimising disease risk and designed specifically for their breeds.

We believe dog breeders in the UK and across the world want to produce happy, healthy puppies. We are confident that breeders will make the most of the scientific developments that we are creating to ensure we are all able to meet this goal.

## Acknowledgements

We would like to thank all the breed clubs, societies, individuals and veterinary surgeons - both at the AHT and at other practices - who have helped contribute to our progress and achievements. Without your support, information and samples, we would not have been able to produce the DNA tests and diagnostic tools.

On many of the individual projects, within the KCGC at the AHT, we have collaborated with scientists and veterinary professionals working elsewhere. These include:

Dr David Sargan (Cambridge University), Dr David Gould (Davies Veterinary Specialists), Professor John Woolliams (The Roslin Institute and the Royal Dick School of Veterinary Medicine) and Professor Jacques Penderis (University of Glasgow School of Veterinary Medicine).

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## Published papers

The research and science being undertaken in the KCGC is published widely to the scientific and veterinary professions through peer-reviewed papers.

This process ensures the highest standards of scientific accuracy and gives credibility to any developments.

Since the development of the KCGC at the AHT, scientists working within the Centre (highlighted in bold) have published 13 peer-reviewed papers detailing the work of the KCGC. These are detailed below:

1. Gould D, **Pettitt L**, **McLaughlin B**, Holmes N, Forman O, Thomas A, Ahonen S, Lohi H, O'Leary C, Sargan D, **Mellersh CS**. *ADAMTS17* Mutation Associated With Primary Lens Luxation Is Widespread Among Breeds. *Veterinary Ophthalmology* in press
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5. Farias FH, Johnson GS, Taylor JF, Giuliano E, Katz ML, Sanders DN, Schnabel RD, McKay SD, Khan S, Gharahkhani P, O'Leary CA, **Pettitt L**, Forman O, **Boursnell M**, **McLaughlin B**, Ahonen S, Lohi H, Hernandez-Merino E, Gould DJ, Sargan D, **Mellersh CS**. An *ADAMTS17* Splice Donor Site Mutation in Dogs with Primary Lens Luxation. *Investigative Ophthalmology and Visual Science.* 2010; 51: 4716-4721
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9. **Lewis TW**, **Blott SC**, Woolliams JA. Genetic evaluation of hip score in UK Labrador Retrievers. *PLoS One* 5 2010b; (10):e12797

10. **Lewis T**, Swift S, Woolliams JA, **Blott S**. Heritability of premature mitral valve disease in Cavalier King Charles spaniels. *Vet J. Epub ahead of print*. 2010c
11. **Lewis T**, Rusbridge C, Knowler P, **Blott S**, Woolliams JA. Heritability of syringomyelia in Cavalier King Charles spaniels. *Veterinary Journal*. 2010d; 183(3):345-347
12. Miyadera K, Kato K, Aguirre-Hernández J, Tokuriki T, Morimoto K, Busse C, Barnett K, Holmes N, Ogawa H, Sasaki N, **Mellersh CS**, Sargan DR. Phenotypic variation and genotype-phenotype discordance in canine cone-rod dystrophy with an *RPGRIP1* mutation. *Mol Vis*. 2009; 15: 2287-305.
13. **Mellersh CS**, **McLaughlin B**, Ahonen S, **Pettitt L**, Lohi H, Barnett KC. Mutation in *HSF4* is associated with hereditary cataract in the Australian Shepherd. *Vet Ophthalmology*. 2009; 12:372-8.