



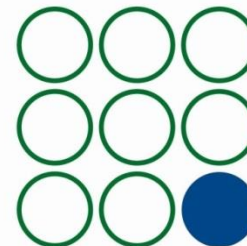
Complex Disease Research at the AHT

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THE KENNEL CLUB

GENETICS CENTRE

AT THE ANIMAL HEALTH TRUST





Talk Layout

- AHT and KCGC background
- Give a Dog a Genome project
- Complex Disease overview
- Complex Disease team focus and experimental approach



Animal Health Trust

- The Animal Health Trust is a **registered charity** that works to reduce the impact disease and injury have on the welfare of companion animals
- Founded in 1942 by a vet, Reginald Wooldridge
- He wanted to apply the same advances being made in human medicine to veterinary medicine through **research**, in order to improve the health and welfare of animals
- It has an **active research unit** that focuses on inherited and infectious diseases
- It provides a **clinical referral service** for veterinary surgeons in practice: dermatology, internal medicine, **neurology**, oncology, **ophthalmology**, orthopaedics, soft tissue surgery, hydrotherapy and physiotherapy
- Over 200 veterinary surgeons, scientists and support staff



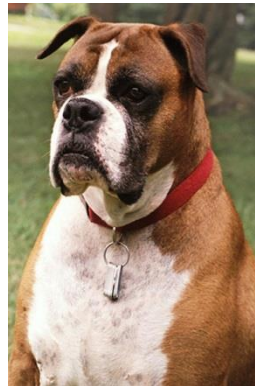
Kennel Club Genetics Centre at the AHT

- Our **primary aim** is to improve the health and welfare of dogs
- Research investigating the **genetic cause** of a variety of inherited diseases in the dog
- Diseases that we study are brought to our attention by breeders or clinicians, and that are debilitating and serious and/or affect large numbers of dogs
- The diseases we study include those which are **painful, cause visual impairment**, require **surgical or medical intervention** or otherwise **reduce the quality or length of life** of affected dogs
- An **immediate-term objective** of our research is to develop **DNA tools** that **dog breeders** can use to reduce the incidence of disease in future generations of dogs and that **veterinary surgeons** can use to help diagnose disease
- A **longer-term aim** is for our findings to improve our understanding of the biology underlying disease in dogs and other species



Canine Reference Genome

- In **2004** the Canine Genome Sequencing Project produced a high-quality draft sequence of a female boxer named Tasha, known as **CanFam1.0**
- By comparing Tasha with many other breeds, the project also compiled an initial set of ~2.5 million single nucleotide polymorphisms (SNPs)
- The current version of the **canine reference genome** is **CanFam3.1**





Variation



- There is a **lot** of variation within the canine genome
- Most of that variation is **neutral**
- Some of the variation is **positive**, or **advantageous**
- Some of the variation is **deleterious (contributes to risk of disease)**
- The challenge is to identify the deleterious variants within all the background, non-deleterious variation





Give a Dog a Genome

- **77** breeds have signed up to GDG since its official launch
- **All** have donated at least **£1000**
- Some breeds have elected to have more than one genome sequenced
- The KCCT has donated a further **£25,000** to support this project...
- ...taking total raised **>£150,000**
- We have now sequenced **89** genomes
- Sequence analysis is well underway





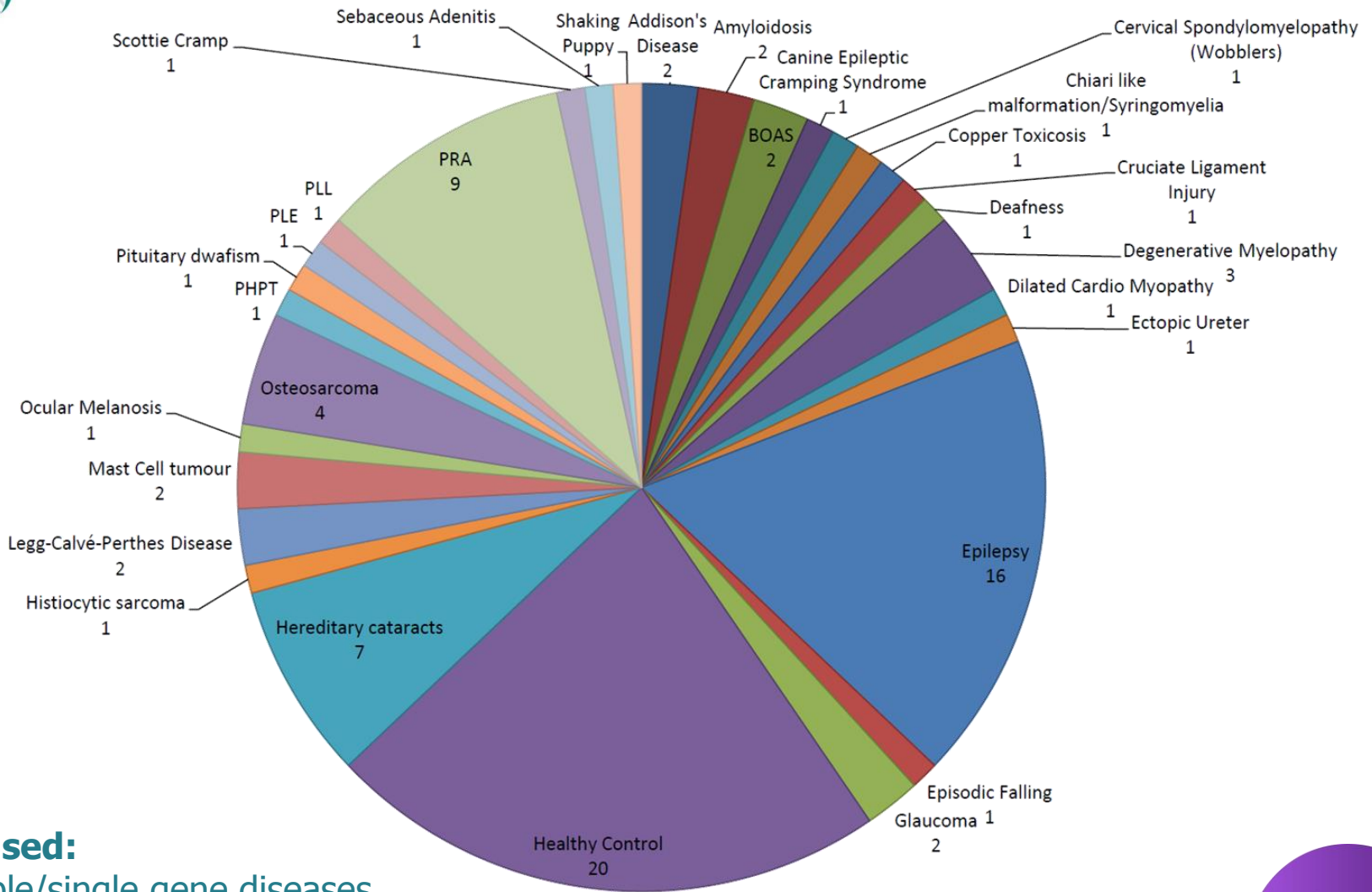
Give a Dog a Genome

- **69 affected** with a disorder that is a demonstrable health concern in the breed
- **20 healthy controls**
- Analysis of some genomes is being undertaken at the AHT
- Data from **29** dogs have been shared with **17** research groups from Europe and USA





Sequenced Dogs



Prioritised:

- Simple/single gene diseases
- Complex diseases AHT currently working on
- Diseases that researchers at other institutions currently working on





Simple/single gene diseases

- Diseases caused by a (single), high impact variant/mutation
- Diseases follow a very characteristic inheritance pattern in families
- Causal mutations can be identified with a small number of cases – because they all share the same mutation.





Complex Disease Team

Complex disease definition:

- Multiple variants, in more than one gene, can combine to cause increased risk of disease
- Environmental factors also contribute to risk – for example may be a trigger for disease onset if an individual has a set of risk variants

Aim of research:

- To develop predictive tools to identify dogs at greater risk of these diseases
- To better understand the biology underlying disease development

Objectives:

- Large-scale sample collections
- Genome scans (genome-wide association studies) and whole genome sequencing

Current focus:

- Neurological diseases - idiopathic epilepsy, movement disorders
- Hereditary cataract
- Diseases with an immune component - polymyositis in Hungarian Vizslas

Sample collection

Cases (Dogs with the disease):

- Breed surveys
- Review of cases by veterinary neurologist
- Clinical characterisation of disease by specialist clinicians
- Estimation of prevalence in breed

Controls (Dogs without the disease):

- Unaffected dogs over the typical age of onset and of the same breed

Case collections:

- Submitted during consultation with specialist clinicians
- Submitted directly by owner with epilepsy questionnaire
- Kennel Club mailing

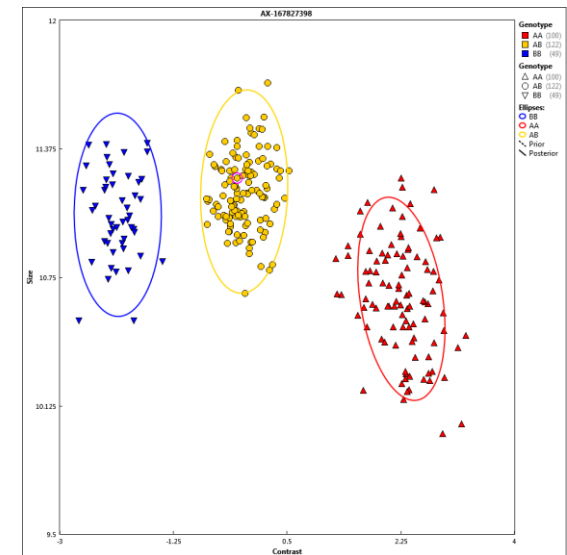
Control collections:

- Submitted directly by owner
- Kennel Club mailings
- Dog shows
- Breed health days



Genome-wide association study

- Enabled by the availability of the canine genomic sequence and the development of high density marker arrays
- Scan the entire genome for regions associated with disease
- Require no prior knowledge of genes associated with disease
- Utilises a set of individuals affected with a particular disease (cases) and individuals clear of the disease (controls)
- Relatively quick to conduct once a robust set of samples is obtained
- Aim for 96 cases and 96 controls



Potential outcomes

- Identification of set of genetic variants that are reproducibly associated with risk of a disorder for a particular breed
- Development of a genetic risk score that identifies individuals in a population at greatest genetic risk of disease
- Integration of this information into breeding tools
- Better understanding of the biological processes underlying the disorder
- Better treatments/diagnosis