Epilepsy and genetics

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Scope of Lecture

- What is a seizure?
- Treating idiopathic epilepsy
- Introduction to genetics
- Genetics of Idiopathic epilepsy

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What is a seizure?

Abnormal brain electrical activity

Sudden episodic transient neurological signs

- Involuntary muscle movements
- Sensory disturbances
- Altered consciousness

Paroxysmal discharge
What is a seizure?

Generalised tonic clonic seizure
Seizure type depends source
Focal seizure

USA study 79% affected Vizsla

- Limb / head tremors
- Staring
- Pupillary dilatation
- Facial twitching
- Lip smacking
- Salivation
- Vomiting
- Without loss of consciousness

May progress to a generalised seizure

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Causes of seizures

- Intracranial causes (in the brain)
  - Primary epilepsy (Idiopathic/genetic)
  - Secondary epilepsy (Acquired /Seizure focus)
  - Static brain disease (e.g. scar after trauma)
  - Progressive brain disease (e.g. brain tumour)

- Extracranial causes (in the blood)
  - Outside
    - Poisons
    - Liver disease
    - Kidney disease
    - Other metabolic disease
  - Inside
    - Excess/Deficit
    - Glucose
    - Electrolytes
    - Triglycerides

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Idiopathic epilepsy

- **Definition**
  - Unknown cause other than possible hereditary predisposition; not in consequence of some other disease or injury

- **Majority genetic (i.e. inherited) in the dog**
  - Prevalence 0.62% general canine population first opinion veterinary practice
  - Breed epilepsy prevalence greater than 1-2% suggests inherited tendency
Top epilepsy “breeds” (UK) (ranking in number registrations KC 2011)

- Labrador retriever (1)
- Border Collie
- German Shepherd (4)
- Staffordshire Bull Terrier (8)
- Crossbreeds
  - Cavalier King Charles Sp. (6)
  - Cocker Spaniel (2)
  - Springer Spaniel (3)
  - Boxer (11)

Also in top 10 for epilepsy Sweden

- Jack Russell Terrier
- Golden Retriever (5)
- Border Terrier (7)
- Yorkshire Terrier (18)
- Dalmatian

Characteristics of epileptic episodes in UK dog breeds: an epidemiological approach


Veterinary Record (2011) 169, 48
doi: 10.1136/vr.d1901

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Vizsla 8/1260
(0.6% epileptic dog population)

<table>
<thead>
<tr>
<th>Breed</th>
<th>Number (%)</th>
<th>Breed</th>
<th>Number (%)</th>
<th>Breed</th>
<th>Number (%)</th>
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<td>Sheepdog (old English)</td>
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<td>Labrador (retriever)</td>
<td>139 (11.0)</td>
<td>Shih tzu</td>
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<td>5 (0.4)</td>
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<td>7 (0.6)</td>
<td>Spaniel (Cavalier King Charles)*</td>
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<td>Lurcher</td>
<td>10 (0.8)</td>
<td>Spanish (cockers)*</td>
<td>26 (2.1)</td>
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<td>Munsterlander</td>
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<td>Spanish (Irish water)</td>
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<td>Bichon frise</td>
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<td>Pinscher (miniature)</td>
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<td>Terrier (Airedale)</td>
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<td>Bouvier des Flandres</td>
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<td>Pointer (English)</td>
<td>6 (0.5)</td>
<td>Terrier (border)*</td>
<td>27 (2.1)</td>
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<td>Boxer*</td>
<td>29 (2.3)</td>
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<td>7 (0.6)</td>
<td>Terrier (Cairn)</td>
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<td>Terrier (miniature bull)</td>
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<td>132 (10.5)</td>
<td>Retriever (flat coat)</td>
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<td>Dogue de Bordeaux</td>
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<td>Terrier (West Highland white)</td>
<td>14 (1.1)</td>
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<tr>
<td>German shepherd dog†</td>
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<td>Terrier (Yorkshire)*</td>
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<td>Viszla (Hungarian)</td>
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<td>Setter (red)</td>
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<td>Whippet</td>
<td>5 (0.4)</td>
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<tr>
<td>Husky (Siberian)</td>
<td>1 (0.1)</td>
<td>Setter (red and white)</td>
<td>1 (0.1)</td>
<td></td>
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</tr>
</tbody>
</table>

* Top 14 breeds accounting for more than 75 per cent of the epileptic cohort
† Top five breeds accounting for more than 50 per cent of the epileptic cohort
What is idiopathic / inherited epilepsy?

Ion channel disorders?

Excitation (more positive charge) - nerve cell more likely to fire

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Diagnostic approach

- History
- Clinical and neurological examination
- Rule out “in blood” causes
  - Blood tests +/- urinalysis
- Rule out “brain” causes
  - Repeat neurological examination
  - Diagnostic imaging (CT and MRI)
  - Testing for metabolic disorders
  - DNA testing?
  - EEG?
To MRI or not to MRI

• Advantage
  – Rules out the “nasties”
  – Can help with decision making for treatment

• Disadvantage
  – Expensive
  – Not a specific test for inherited epilepsy
  – For animals with inherited epilepsy does not necessarily help with prognosis or treatment
  – Requires general anaesthetic
Epilepsy specific protocol -demonstrating encephalitis
IDIOPATHIC EPILEPSY

Canine idiopathic epilepsy

Clare Rusbridge

Canine idiopathic epilepsy has an estimated prevalence of 0.62 per cent in primary veterinary practice (Kearsley-Fleet and others 2013) and as such is one of the most common chronic neurological diseases. Descriptions of ‘epilepsy of unknown origin…where no symptom characteristic of any other condition has as yet presented’ can be found in early veterinary textbooks (Kirk 1982) and although our knowledge is now considerably to start treatment in a patient that is at high risk of further seizures, eg, following a cerebral vascular accident.

- Idiopathic epilepsy is defined as epilepsy of unknown cause other than possible
Treatment of Epilepsy

Dx Epilepsy

- Single Seizure
  - ≥2 week or more interictal period
  - Imepitoin 10-20mg/kg BID
  - Unacceptable seizure control

- Cluster Seizures
  - and/or < 2 week interictal period
  - Phenobarbital 3mg/kg BID
  - 1-2 weeks
  - Serum phenobarbital concentration aim 100-140μmol/l (20-28μg/ml)
Seizure control unacceptable

- Consider Imepitoin 30mg/kg BID
- Combination Phenobarbital 3mg/kg BID, Imepitoin 10-20mg/kg
  - If seizure control acceptable continue
    - If Imepitoin first therapy then consider withdrawing and continuing phenobarbital monotherapy
  - Unacceptable seizure control
    - Add Potassium bromide 30-40mg/kg per day
    - Withdraw Imepitoin
Seizures not controlled?

- Ensure blood concentrations adequate
- Increase current therapy
- Switch to different primary drug combination
- Add or switch to novel antiepileptic drug
  - Propentofylline
  - Topiramate
  - Zonisamide
  - Levetiracetam
  - Gabapentin
  - Pregabalin
Inherited disease

- Simple (single gene)
  - e.g. urate stone disorder
- Complex
  - e.g. idiopathic epilepsy
- Susceptibility to immune mediated disease
  - e.g. Vizsla inflammatory polymyopathy
- Inherited susceptibility to neoplasia
  - e.g. brain tumour  Boxer dogs
Single gene disorder
Simple autosomal recessive

Unaffected Carrier Sire + Unaffected Carrier Dam

25% Clear Offspring
50% Carrier Offspring
25% Affected Offspring
Commercial DNA test

LABOKLIN has over 15 years experience in animal genetic testing. We provide extensive range of genetic tests covering large number of breeds. We develop our own testing techniques that implements the latest advances in molecular biology to provide reliable, accurate and precise results.
Breed wide testing

**Case study**

**“We’ve come such a long way”**

Dachshund lover **Gill Key** explains how owners, breeders, breed clubs, disease researchers and the Kennel Club are working together to help defeat a serious inherited condition, known as Lafora.

I don’t show or breed, but I’ve loved and owned Dachshunds for many years. Unfortunately my first Miniature Wire-Haired Dachshund (MWHD), Alfie, succumbed to a condition I eventually discovered was called Lafora – an inherited form of late onset epilepsy.

Lafora, or as I now know, cerebellar myoclonus jerking, full and partial seizures, panic attacks, blindness and dementia, is caused by the dog’s inability to metabolise starch into sugar, and so insoluble amyloid plaques build up in the central nervous system, gradually causing it to deteriorate.

Conea Lafora’s Disease was first described in 1996 by Sue Fitzmaurice, a veterinary neurologist, but it was another neurologist, Dr Cleve Rodridge who, having diagnosed several cases in referred MWHDs in the early 2000s, put two and two together when the read up on Dr Barge’s description of the Sick-breeding collaboration between human and veterinary medicine. The two UK veterinary neurologists collected more DNA samples and pedigrees information from a small group of MWHD breeders, which also proved vital in Dr Minnissian’s painstaking research. However, it wasn’t until 2005 that he published his conclusions – he had identified a genetic mutation that was causing the symptoms in the dogs, and for the first time a link between such a mutation and epilepsy was proven.

**VITAL RESEARCH**

The Dachshunds’ DNA samples proved vital in moving the human research on, and today the Canadian team are looking into a number of promising gene therapies to help ease affected teenagers’ symptoms, and, in due course, contacine symptoms too. Less positively, the Canadians’ offer of further genetic screening of UK MWHDs was rejected.

I was horrified when, in early 2005, I started to have regular fits. My vet put me down to idiopathic epilepsy (epilepsy of unknown cause), but gradually Alfie started to show an odd head-jerking and curious stiff walking gait. I stumbled on a short clip of a MWHD jerking, exactly like Alfie, on Dr Rodridge’s website and the dog was described as having Lafora. The film to my vet and he agreed words, it could not distinguish between clear or carrier dogs.

**DNA TESTING**

Breed clubs have since gathered sufficient funding (over £30,000) from various sources, including the Kennel Club (KC) Charitable Trust, to fund further research, and in summer 2013 Dr Minnissian announced he had developed a full.
Complex inheritance

• Polygenic traits
  – genes interact, or add up, to produce one result

• Multifactorial traits
  – Genetic factors
  – Environmental factors
  – Threshold effect

• Disease occurs when “correct” combination of environment and genetic factors
  e.g. diabetes mellitus
The ChromaGene™ test will determine which one of the genotypes listed below your Labrador Retriever is:

If your dog is black
Possible ChromaGene™ Types are:
I, II, III, IV.

If your dog is chocolate
Possible ChromaGene™ Types are:
VIII, IX.

If your dog is yellow with a black nose
Possible ChromaGene™ Types are:
V, VI.

If your dog is yellow with a liver nose
Your dog is ChromaGene™ Type VII.

Coat Color Inheritance Chart for the Labrador Retriever

<table>
<thead>
<tr>
<th>ChromaGene™ Type</th>
<th>BBEE I</th>
<th>BBEE II</th>
<th>BBEE III</th>
<th>BBEE IV</th>
<th>BBEE V</th>
<th>BBEE VI</th>
<th>bbEE VII</th>
<th>bbEE VIII</th>
<th>bbEE IX</th>
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</thead>
<tbody>
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<td>BBEE I</td>
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<td>All Black</td>
<td>All Black</td>
<td>All Black</td>
<td>All Black</td>
<td>All Black</td>
<td>All Black</td>
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<td>All Black</td>
</tr>
<tr>
<td>BBEE II</td>
<td>All Black</td>
<td>⅔ Black</td>
<td>All Black</td>
<td>⅔ Black</td>
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<td>⅔ Black</td>
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<tr>
<td>bbEE</td>
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<td>⅔ Yellow</td>
<td>All Black</td>
<td>⅔ Yellow</td>
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</tr>
</tbody>
</table>

Coat Colour Labradors
Complex inheritance
selection for desired conformation
Environmental effect?
Wobbler’s syndrome
Caudal cervical spondylomyelopathy

UK Breed standard - neck

Dalmatian - Fairly long, nicely arched, light & tapering. Entirely free from throatiness.

Dobermann - Fairly long and lean, carried with considerable nobility; slightly convex and in proportion to shape of dog. Region of nape very muscular.

Great Dane - Neck long, well arched, quite clean and free from loose skin, held well up, well set in shoulders, junction of head and neck well defined.
Inherited susceptibility to immune medicated disease

Facial tumour Tasmanian devil
Inherited susceptibility to immune mediated disease

• Major histocompatibility complex
dog leukocyte antigen - DLA
  – recognition of self and non-self
  – highly polymorphic genes (i.e. many variations)
• advantage survival against infectious diseases
• females preference for mates with dissimilar MHCs
• selective inbreeding restriction DLA haplotypes
  – susceptibility to infectious diseases
  – susceptibility to immune mediated conditions
Pug encephalitis

- susceptibility associated DLA region chromosome 12
- female, fawn, < 7y predisposed
- 2 copies = 12.75 x more likely Pug encephalitis
- Breeders advised to avoid breeding dogs with 2 copies gene.
Genetic susceptibility
Cancer

Gliomas – Boxer dogs
Genetics of Idiopathic epilepsy

The challenge of finding the genes in a complex disorder

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Heritability of epilepsy

- Most epileptic dogs do not have epileptic parents and epilepsy can skip generations
  - *Autosomal recessive*
  - *Unaffected dogs may be carriers*
- Often high e.g. Irish Wolfhounds = 0.87
  - if one knew what to select for it could be “bred out”
  - Disease may be influenced by other as yet unknown factors
  - More than one gene
Vizsla Epilepsy Research Project

In March of 1999, the AKC Canine Health Foundation (AKC CHF) awarded a grant of $57,500.00 to researchers led by Dr Ned Patterson at the University of Minnesota College of Veterinary Medicine to study the molecular genetics of canine epilepsy in Vizslas, English Springers and Beagles. Since then, the project expanded to include Australian Shepherds and Greater Swiss Mountain Dogs. The goal of this study is to identify multiple genetic markers for epilepsy and to develop a screening test to determine normal, carrier and affected status, thus allowing breeders the potential to eliminate epilepsy from breeding stock.

In the fall of 2014, the AKC CHF awarded Dr. Ned Patterson’s team at the University of Minnesota an additional $104,781.00 to identify genetic variants, biomarkers and new therapies. Under the guidance of Dr. Ned Patterson, a collaborative group proposes to evaluate traditional DNA genetic markers, blood biomarkers called microRNAs (miRNAs), and potential new drugs for the emergency treatment of seizures in dogs. This phase of the research will focus on the Vizsla and the Australian Shepherd. The VCA Welfare Foundation is proud to be a Charter Sponsor of this research. Read the grant announcement here.

The success of this research is dependent on collecting good samples from our Vizsla population. Dr. Patterson’s team is actively seeking samples from affected (seizing) dogs, related family members (Eg., dam, sire, litter mates) as well as samples from non-affected (controls) dogs who are 8 years and older.

To participate, please visit the Epilepsy Research Initiative page on the University of Minnesota website: http://www.cvm.umn.edu/vbs/faculty/Mickelson/lab/ie/home.html

Here you can download Sample Submission Instructions and complete an online survey for affected dogs. To print the survey, click here.

If you have any questions or need assistance completing the forms or pedigrees, please contact Katie Minor at the Canine and Equine Genetics Lab at the University of Minnesota at minork@umn.edu.
Finding generalised IE genes
Work in progress for many breeds
http://www.canine-epilepsy.net/

- 9909 DNA samples (28/1/11)
  - 108 different breeds
  - 1578 affected dogs
- University of Missouri
- University of Minnesota
  - Australian Shepherds, Beagles,
  - English Springer Spaniels
  - Greater Swiss Mountain Dogs, Vizslas

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Canine epilepsy - no easy answers

• ? link between and a few specific genes
  – CACNB1 Vizsla
  – CHRNB2 Greater Swiss Mountain Dog
  – KCNQ3 and LGI1 Beagle

• Not causal

• canine epilepsy due multiple genes

Funded AKC Canine Health Foundation

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Genetics of epilepsy is complex

- Different genes influence
  - Tendency for epilepsy
  - Age of onset
  - How bad it is
  - Responsiveness to drugs
- If we understood the genetics
  - We could prevent epilepsy
  - Find better ways of treating it
How do you tackle complex inherited disease in a breed?

• Don’t breed from affected dogs
  – But what if first signs are at 5 years plus?
• Find the gene(s) !!!
  – Good phenotyping
  • good controls
  • Accurate diagnostic tests
  – Submit left over blood from diagnostic tests
• Breeders, vets and researchers must work together
Problem - Age of Onset of Epilepsy
Irish Wolfhounds

1st seizure by 3yrs in 82% bitches
4yrs in 83% dogs
Age of Onset of Epilepsy
Belgian Shepherds

mean 3.3 years (range 0.5 – 8.0 years)
Vizsla

- No significant gender predisposition
  - males slightly overrepresented (59%)
- median age seizure onset 3y
Complex inherited disorders
Avoid Matador breeding (popular sire syndrome)
Avoid Matador breeding (popular sire syndrome)

- Widespread dissemination of dog’s genes before long term impact determined
- Avoid overuse of young unproven dogs (< 5y?)
- Scandinavia - no more offspring than equivalent to 5% puppies registered for that breed over 5yrs
- UK Kennel Club
  - “if the sire has been health checked and can produce disease free offspring it is better that it be allowed to continue siring rather than unhealthy sires being used”
  - but no individual can have perfect DNA and most dog health issues are caused by recessive genes!
  - Mate Select program??

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Thank you for listening!

Any questions?