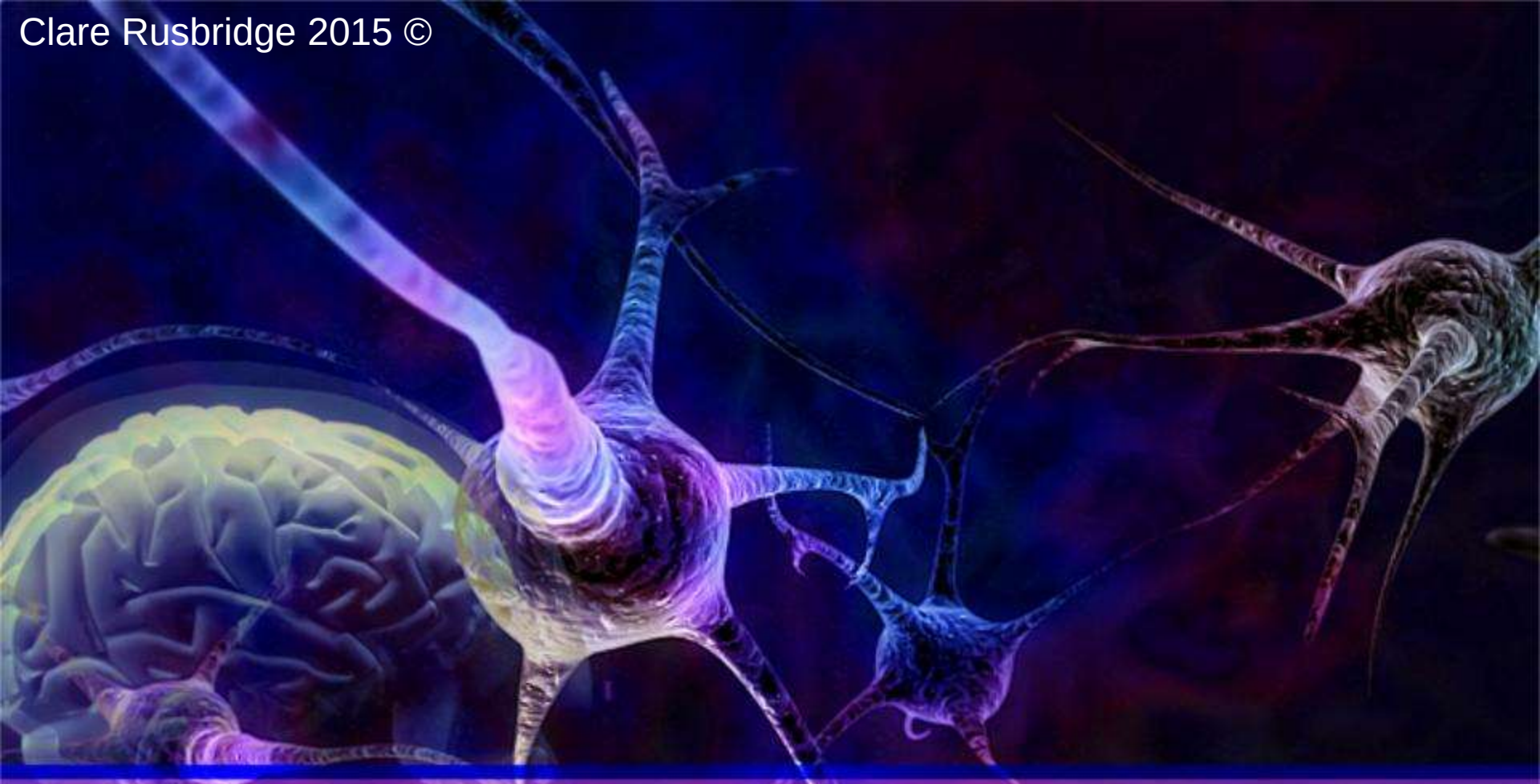


Epilepsy and genetics

Scope of Lecture

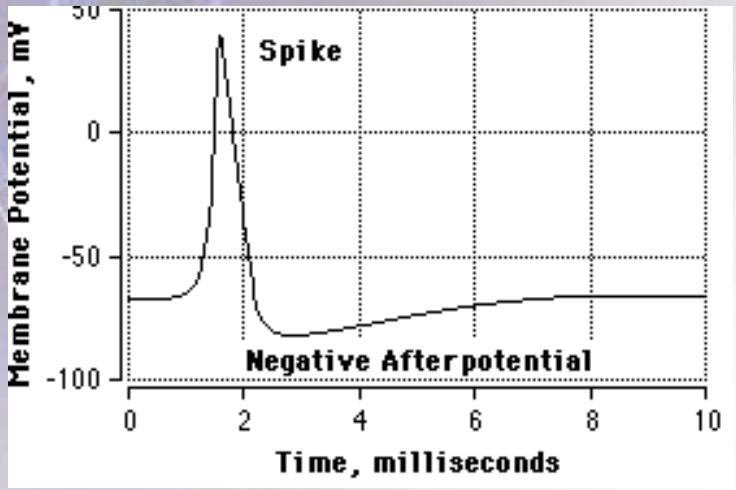
- What is a seizure?
- Treating idiopathic epilepsy
- Introduction to genetics
- Genetics of Idiopathic epilepsy

What is a seizure?

Abnormal brain electrical activity

Sudden episodic transient neurological signs

- Involuntary muscle movements
- Sensory disturbances
- Altered consciousness

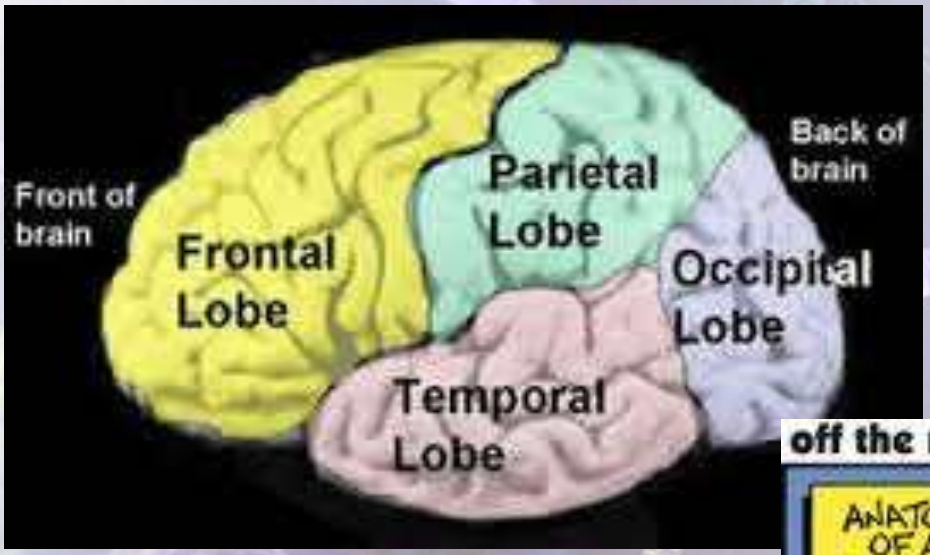


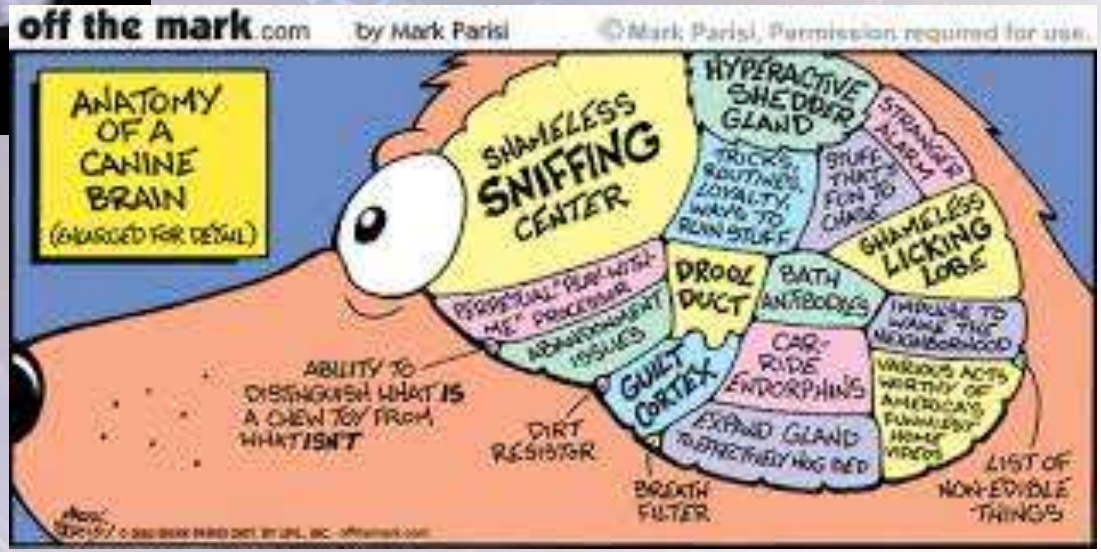
Paroxysmal discharge

What is a seizure?

Generalised tonic clonic seizure

Seizure type depends source





Focal seizure

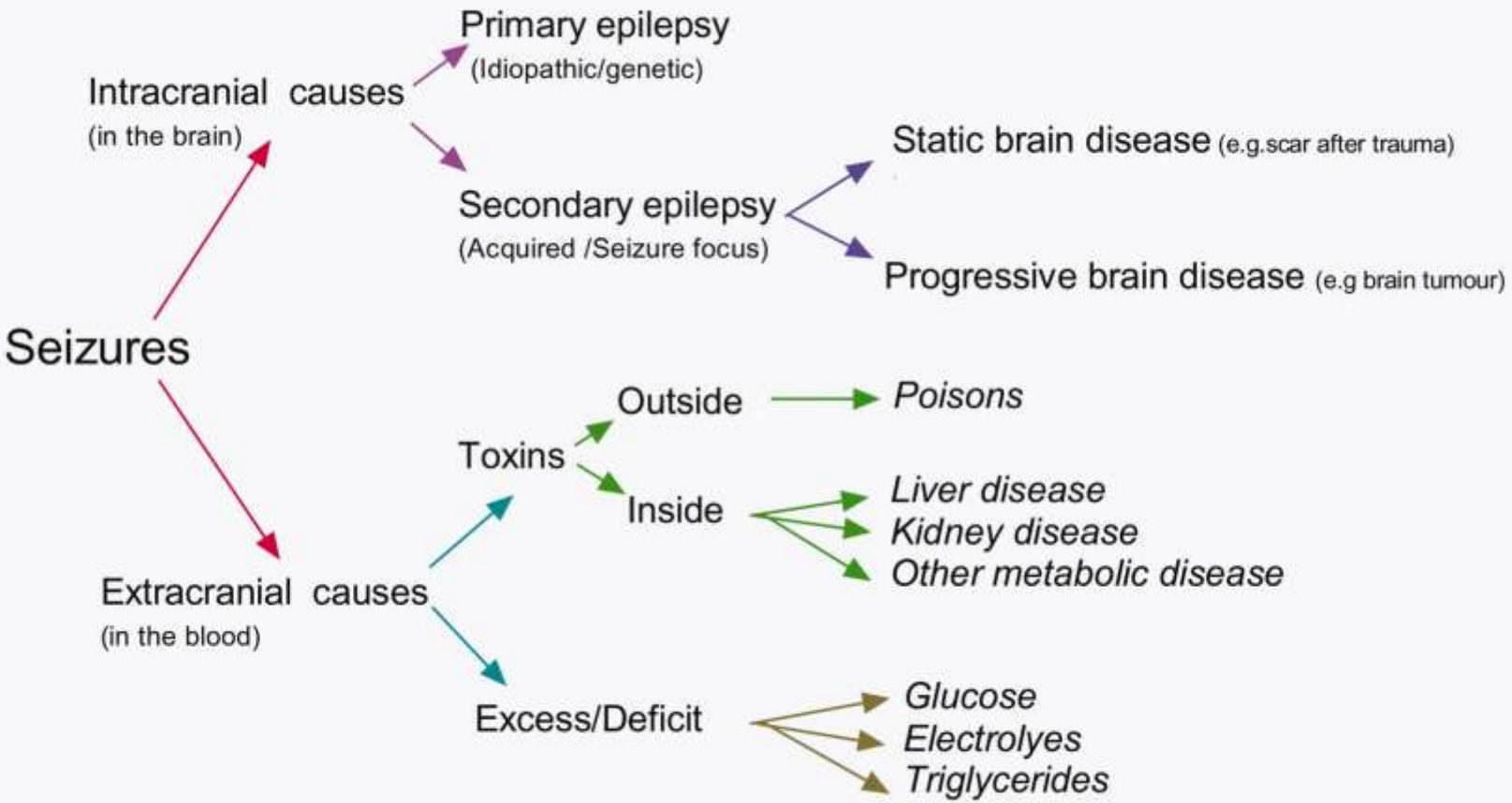
J Vet Intern Med. 2003 May-Jun;17(3):319-25.

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

Causes of seizures

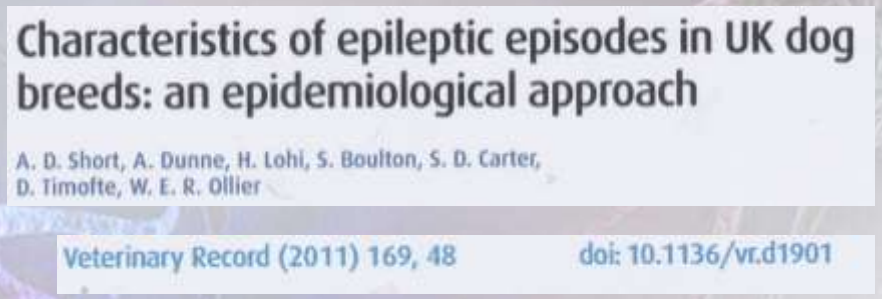


Idiopathic epilepsy

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


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

A. D. Short, A. Dunne, H. Lohi, S. Boulton, S. D. Carter, D. Timofte, W. E. R. Ollier

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

Also in top 10 for epilepsy Sweden

Vizsla 8/1260 (0.6% epileptic dog population)

TABLE 1: Breed distribution of a cohort of 1260 dogs with epilepsy

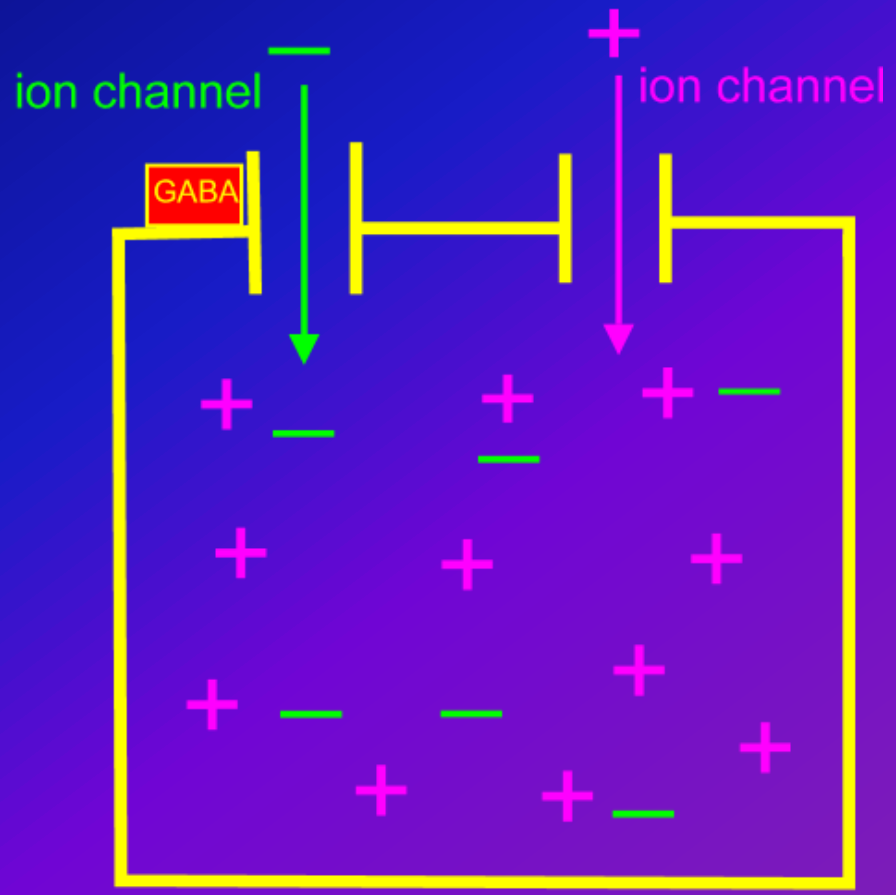
Breed	Number (%)	Breed	Number (%)	Breed	Number (%)
Alaskan malamute	8 (0.6)	Keeshond	3 (0.2)	Sheepdog (old English)	2 (0.2)
Australian shepherd dog	1 (0.1)	Labrador (retriever)*†	139 (11.0)	Shih tzu	5 (0.4)
Basset griffon vendéen	5 (0.4)	Lhasa apso	7 (0.6)	Spaniel (Cavalier King Charles)*	21 (1.7)
Basset hound	3 (0.2)	Lurcher	10 (0.8)	Spaniel (cocker)*	26 (2.1)
Beagle	12 (1.0)	Munsterlander	1 (0.1)	Spaniel (Irish water)	1 (0.1)
Belgian shepherd dog	5 (0.4)	Newfoundland	1 (0.1)	Spaniel (springer)*	29 (2.3)
Bernese mountain dog	1 (0.1)	Northern Inuit	5 (0.4)	Spinone (Italian)	6 (0.5)
Bichon frise	5 (0.4)	Pinscher (miniature)	1 (0.1)	Terrier (Airedale)	1 (0.1)
Bouvier des Flandres	1 (0.1)	Pointer (English)	6 (0.5)	Terrier (border)*	27 (2.1)
Boxer*	29 (2.3)	Pointer (German)	7 (0.6)	Terrier (Cairn)	4 (0.3)
Bulldog	8 (0.6)	Pomeranian	1 (0.1)	Terrier (English bull)	1 (0.1)
Bullmastiff	1 (0.1)	Poodle (miniature/toy)	5 (0.4)	Terrier (fox)	2 (0.2)
Chihuahua	8 (0.6)	Poodle (standard)	9 (0.7)	Terrier (Jack Russell)*	63 (5.0)
Chinese crested dog	5 (0.4)	Pug	3 (0.2)	Terrier (Lakeland)	1 (0.1)
Collie (bearded)	2 (0.2)	Retriever (curly coat)	1 (0.1)	Terrier (miniature bull)	1 (0.1)
Collie (border)*†	132 (10.5)	Retriever (flat coat)	1 (0.1)	Terrier (Norfolk)	1 (0.1)
Collie (rough)	2 (0.2)	Retriever (golden)*	58 (4.6)	Terrier (Norwich)	1 (0.1)
Crossbreed*†	259 (20.5)	Rhodesian Ridgeback	6 (0.5)	Terrier (Patterdale)	5 (0.4)
Dachshund	18 (1.4)	Rottweiler	8 (0.6)	Terrier (Scottish)	4 (0.3)
Dalmatian*	19 (1.5)	Saint Bernard	3 (0.2)	Terrier (Staffordshire bull)*†	66 (5.2)
Doberman	2 (0.2)	Saluki	1 (0.1)	Terrier (Tibetan)	3 (0.2)
Dogue de Bordeaux	1 (0.1)	Schnauzer (giant)	1 (0.1)	Terrier (West Highland white)	14 (1.1)
German shepherd dog*†	82 (6.5)	Schnauzer (miniature)	3 (0.2)	Terrier (Yorkshire)*	39 (3.1)
German spitz	1 (0.1)	Setter (English)	2 (0.2)	Viszla (Hungarian)	8 (0.6)
Great dane	2 (0.2)	Setter (Irish)	8 (0.6)	Weimaraner	7 (0.6)
Greyhound	10 (0.8)	Setter (red)	1 (0.1)	Whippet	5 (0.4)
Husky (Siberian)	1 (0.1)	Setter (red and white)	1 (0.1)		

* 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

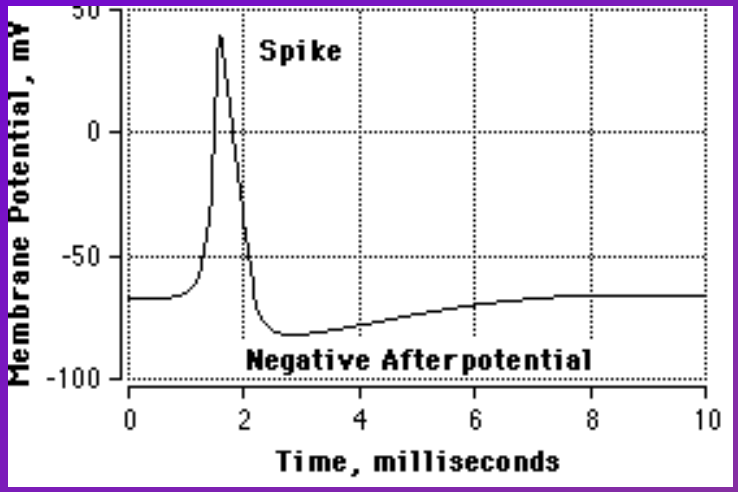
Veterinary Record (2011) 169, 48 doi: 10.1136/vr.d1901

What is idiopathic / inherited epilepsy?

Ion channel disorders?



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



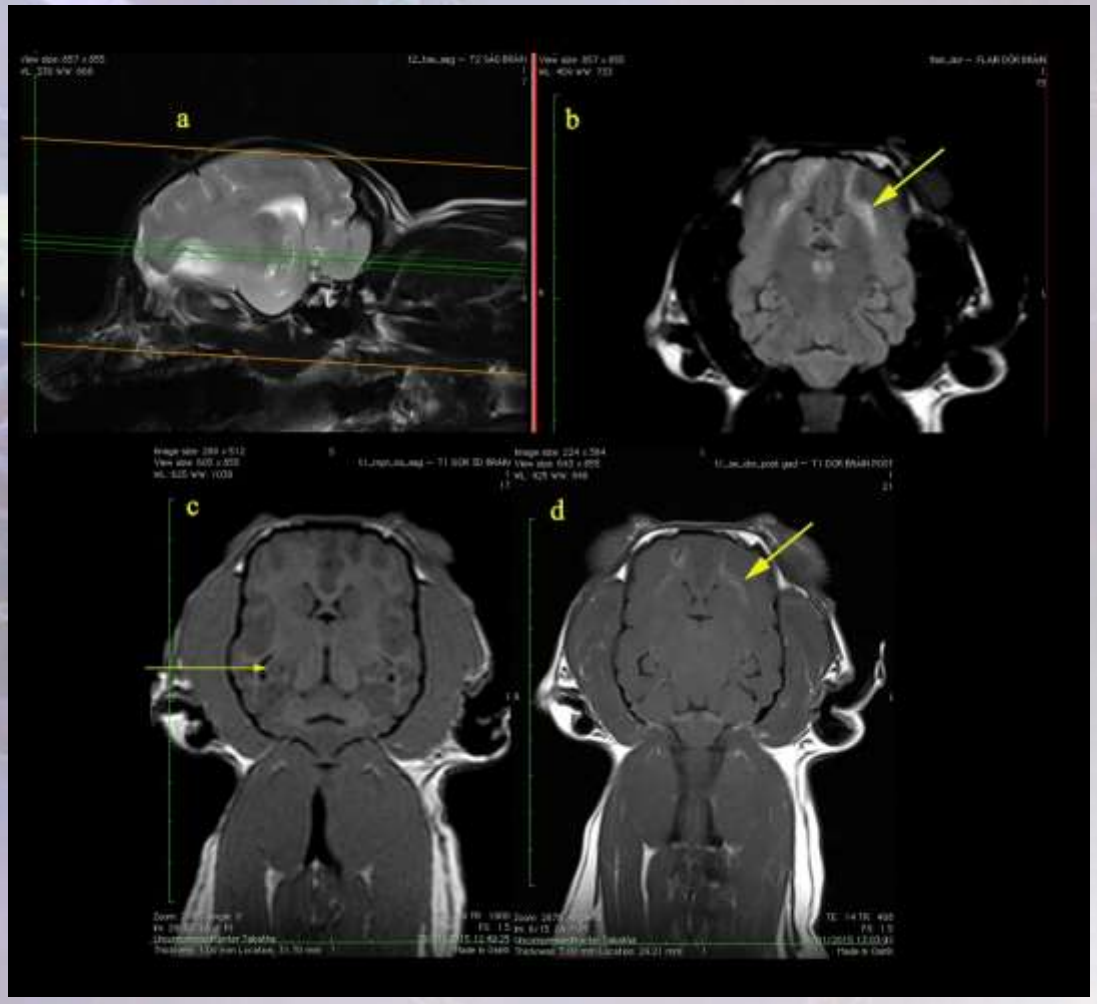
Diagnostic approach

- 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

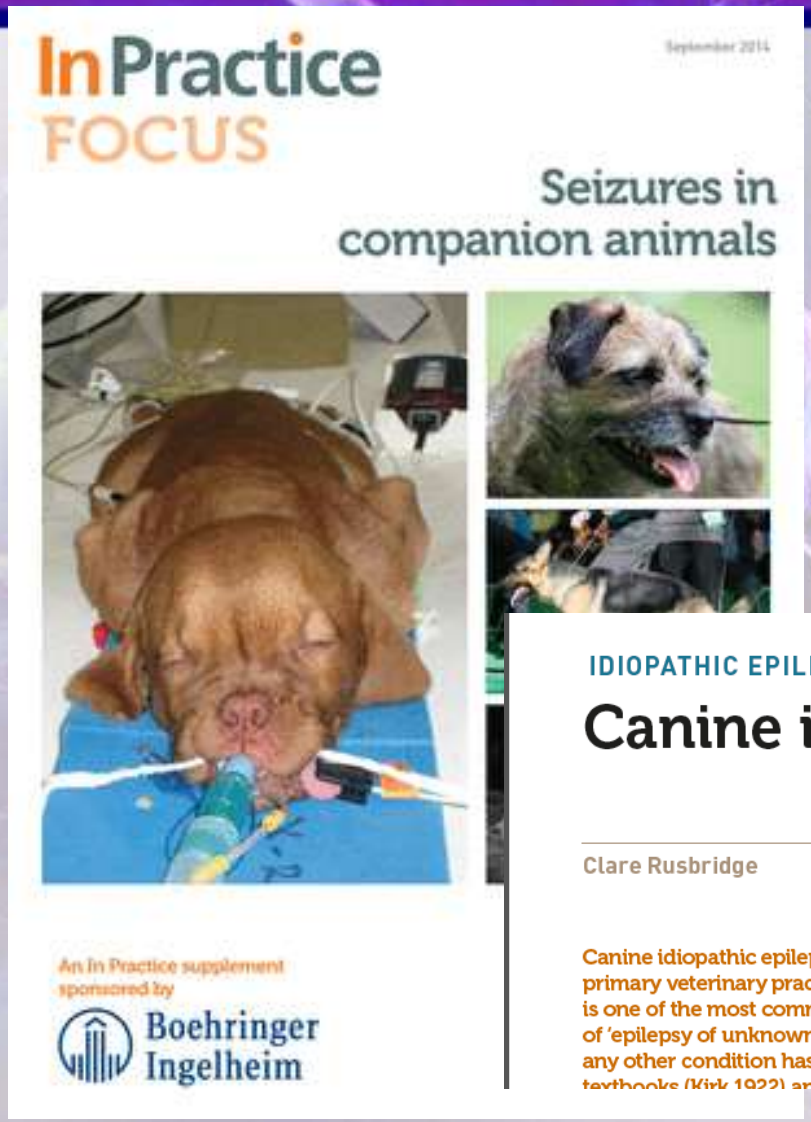
- Advantage
  - Rules out the “nasties”
  - Can help with decision making for treatment
- Disadvantage
  - Expensive
  - Not a specific test for inherited epilepsy
  - For animals with inherited epilepsy does not necessarily help with prognosis or treatment
  - Requires general anaesthetic

Epilepsy specific protocol -demonstrating encephalitis



Lecture notes?

http://inpractice.bmj.com/content/36/Suppl_1.toc



September 2014, Volume 36, Suppl 1

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- Foreword
- Pathophysiology
- Diagnosis
- Idiopathic epilepsy
- Neoplasia
- Juveniles

IDIOPATHIC EPILEPSY

Canine idiopathic epilepsy

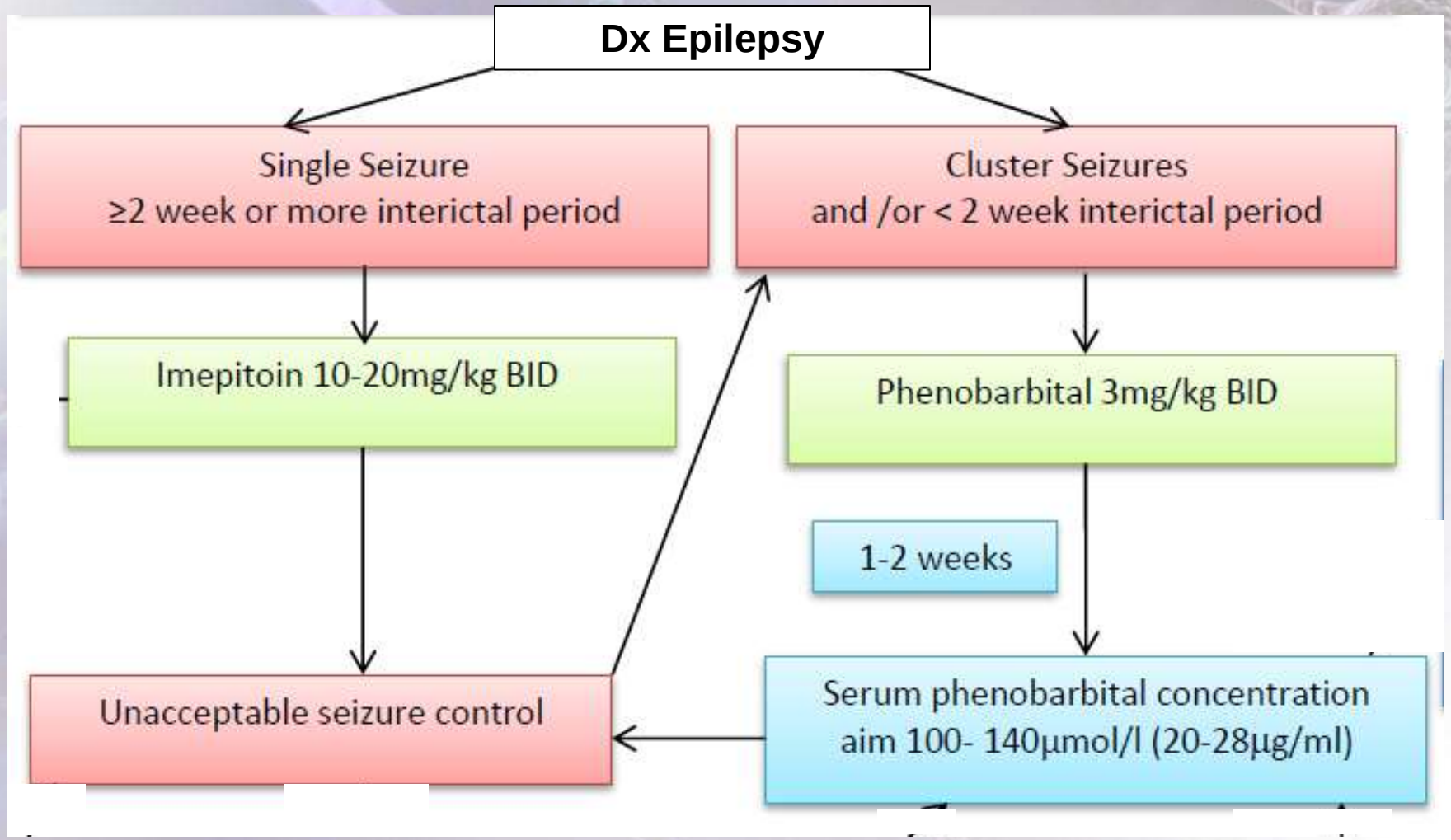
Clare Rusbridge

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 1922) and although our knowledge is now considerably

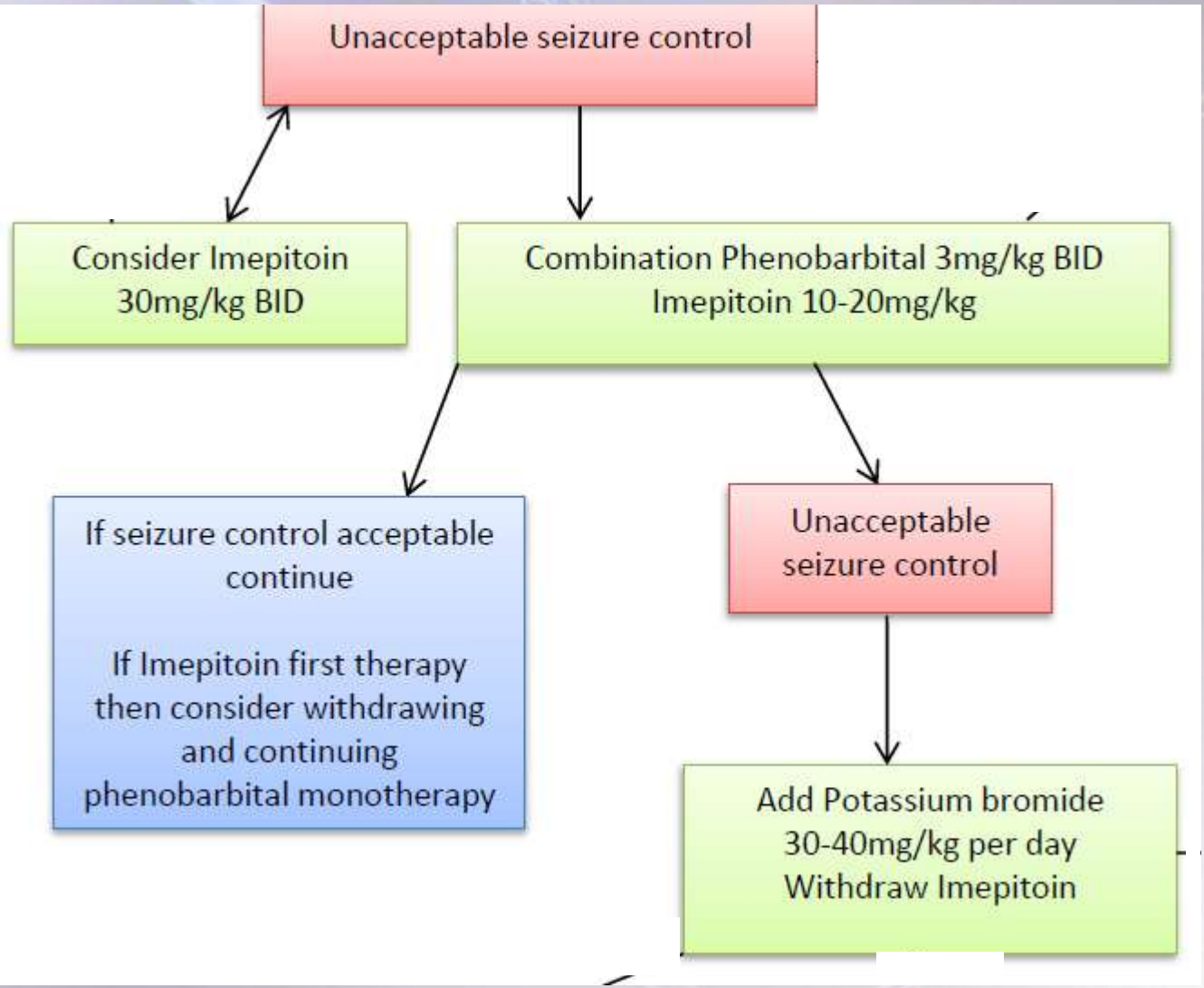
to start treatment in a patient that is at high risk of further seizures, eg, following a cerebral vascular accident.

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

Treatment of Epilepsy

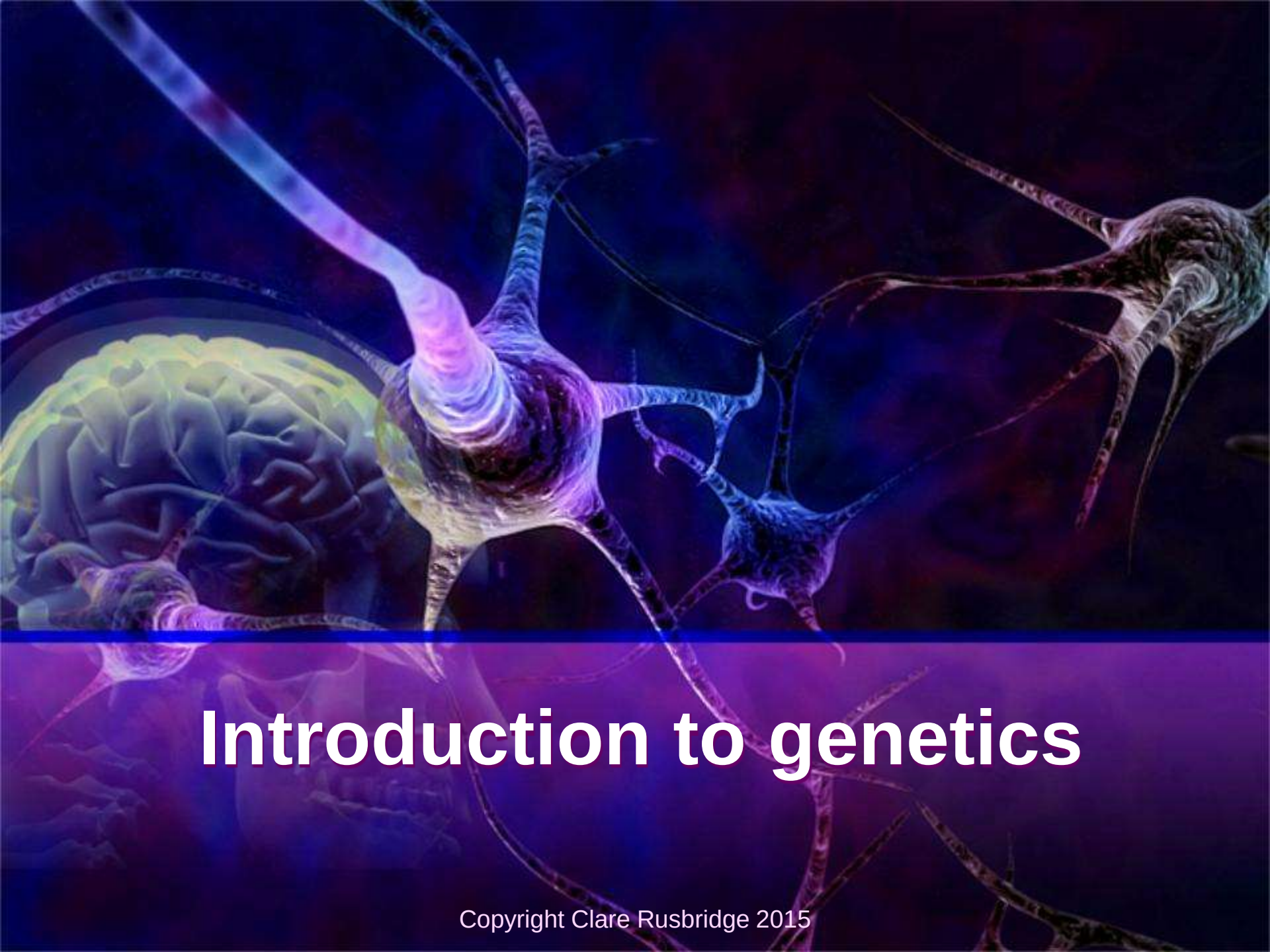


Seizure control unacceptable



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



Introduction to genetics

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

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Genetic Diseases

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.

Dogs	Cats	Horses	Cattle	Pigs
				
Genetic Diseases in Dogs	Genetic Diseases in Cats	Genetic Diseases in Horses	Genetic Diseases in Cattle	Genetic Diseases in Pigs

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, as I now know, causes myoclonus (jerking), full and partial seizures, panic attacks, blindness and dementia. It develops because the dog can't metabolise starch into sugar, and so insoluble starchy platelets build up in the central nervous system, gradually causing it to deteriorate.

Canine Lafora's Disease was first described in 1996 by Sue Fitzmaurice, a veterinary neurologist, but it was another neurologist, Dr Clare Rusbridge who, having diagnosed several cases in related MWHDs in the early 2000s, put two and two together when she read up on Dr Berge Minassian's work at the Sick breaking collaboration between human and veterinary medicine. The two UK veterinary neurologists collected more DNA samples and pedigree information from a small group of MWHD breeders, which also proved vital to Dr Minassian'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, canine symptoms too. Less positively, the Canadians' offer of further genetic screening of UK MWHD

Gill had no idea at first what was making Alfie so poorly.

FIND OUT MORE

- The Canine Epilepsy Support Group, call Anne Morley on 01903 784263 or 785327.
- www.whdc.co.uk/latest-laforas-news.php – to find out how to get your dog tested.
- www.laforadogs.org – for support and advice on coping with an affected dog.
- http://dachshundbreedcouncil.org.uk – for more on Dachshunds.
- www.chelseashope.org – for more on Human Lafora and research.

nd I was horrified when, in early 2005, started to have regular fits. My vet put en down to idiopathic epilepsy (epilepsy unknown cause), but gradually Alf arted to show an odd head-jerking and curious stiff walking gait. I stumbled on short clip of a MWHD jerking, exactly e Alfie, on Dr Rusbridge's website and e dog was described as having Lafora. showed 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 Minassian announced he had developed a full

One emerging worry is the realisation that a number of carrier dogs have been exported over the years, so there is a strong possibility the condition is already present in breeding stock in Australia, Russia and Canada, to name but a few.

Unfortunately some of those puppies will inherit the Lafora gene from both parents, which means their owners could face years of trauma, huge vet bills, and eventually

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 e.g. diabetes mellitus

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Canine

Chro

Canine Tests by Breed

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 yellow with a black nose
Possible ChromaGene™ Types are:
V, VI.

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

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

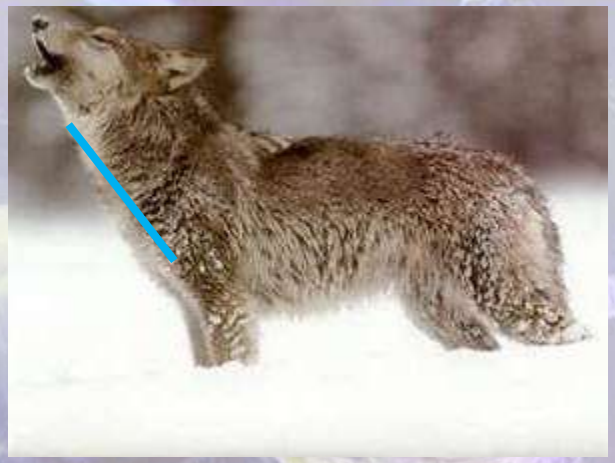
Coat Color Inheritance Chart for the Labrador Retriever

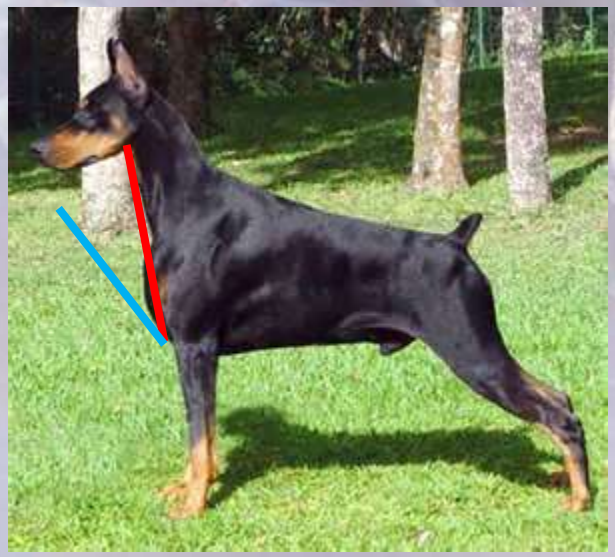
ChromaGene™ Type

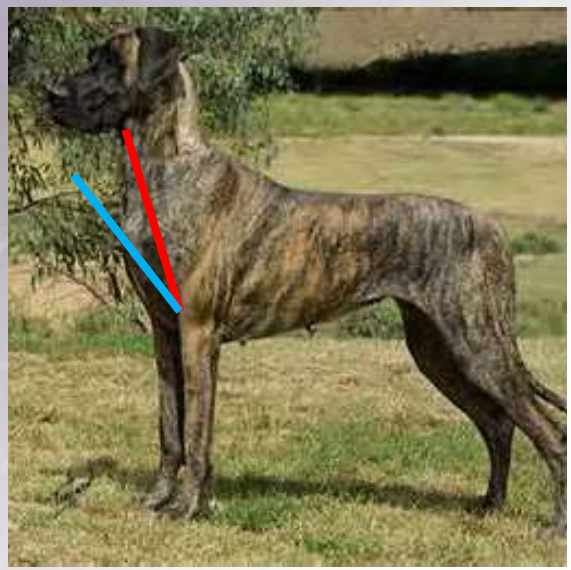
	BBEE I	BBEe II	BbEE III	BbEe IV	BBee V	Bbee VI	bbee VII	bbEE VIII	bbEe IX
BBEE I	All Black	All Black	All Black	All Black	All Black	All Black	All Black	All Black	All Black
BBEe II	All Black	¾ Black ¼ Yellow	All Black	¾ Black ¼ Yellow	½ Black ½ Yellow	½ Black ½ Yellow	½ Black ½ Yellow	All Black	¾ Black ¼ Yellow

Coat Colour Labradors

Complex inheritance
selection for desired conformation



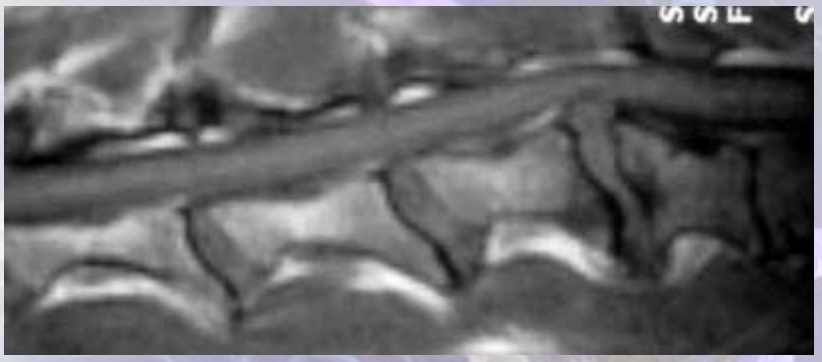




Environmental effect?

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

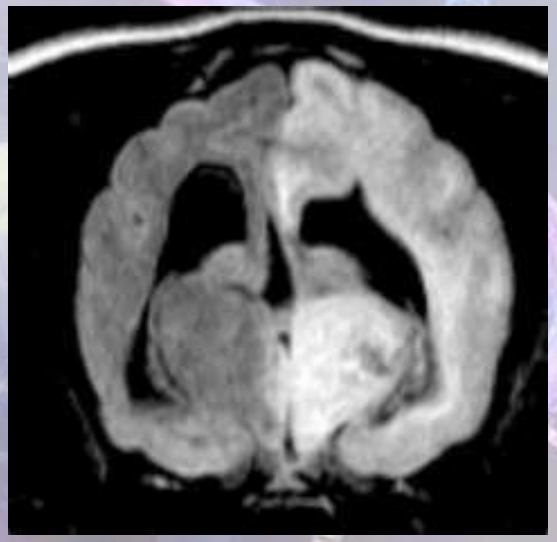
  – highly polymorphic genes (i.e. many variations)

    - 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

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

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Latest News »

April 2015
2015 VCA National Event pre-registration and Merchandise store have now closed
NGDC Results are now posted

March 2015
Information on 2015 NFT
Decade of the Vizsla-scanned book
2015 VCA National Event Deadlines are close soon

February 2015
Check out updates to Specialty Events

» Read all current news

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/

Ned Patterson
Minnesota

- 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

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

Genetics of epilepsy is complex

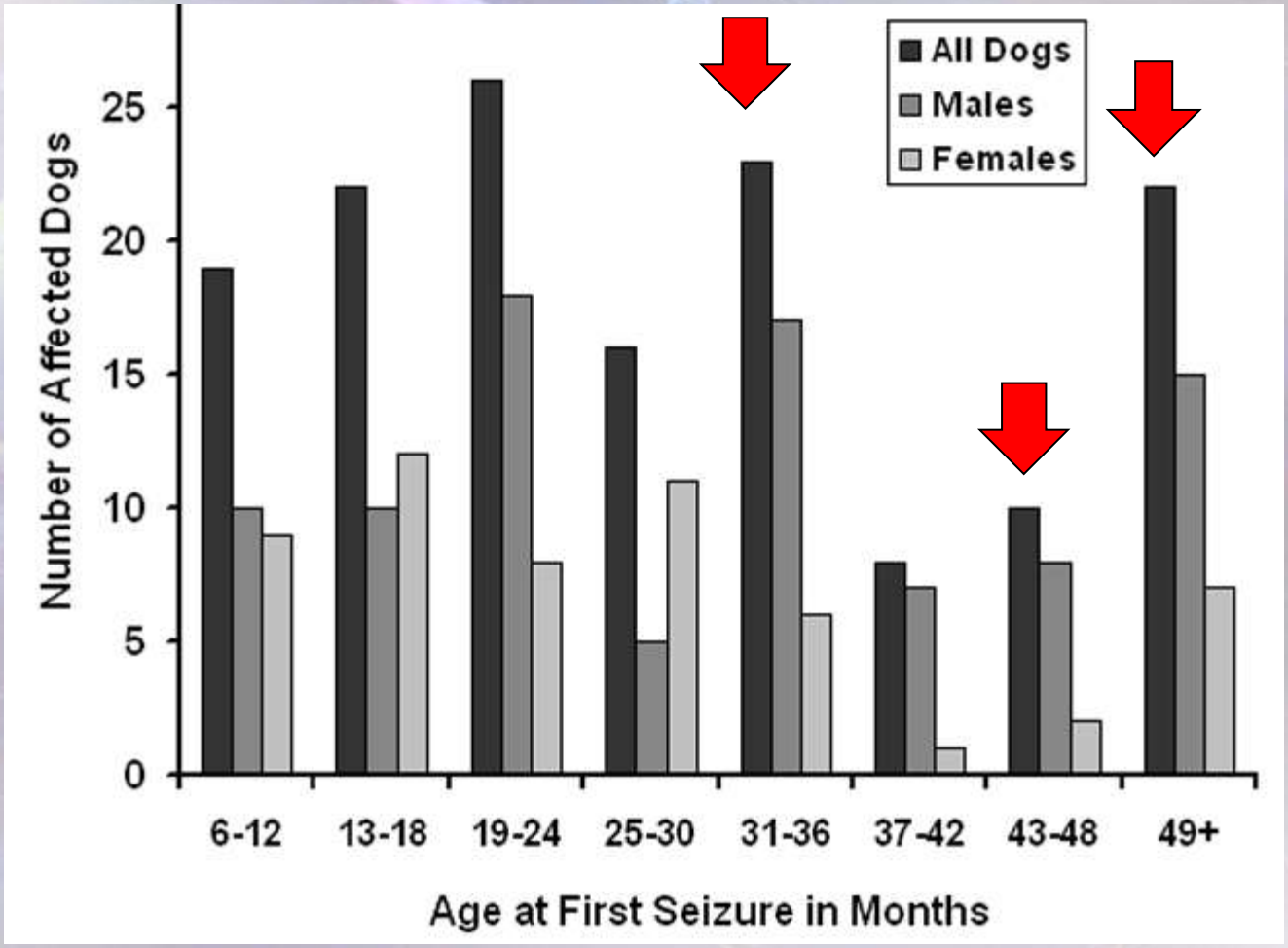
- Different genes influence
  - Tendency for epilepsy
  - Age of onset
  - How bad it is
  - Responsiveness to drugs
- If we understood the genetics
  - We could prevent epilepsy
  - Find better ways of treating it

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



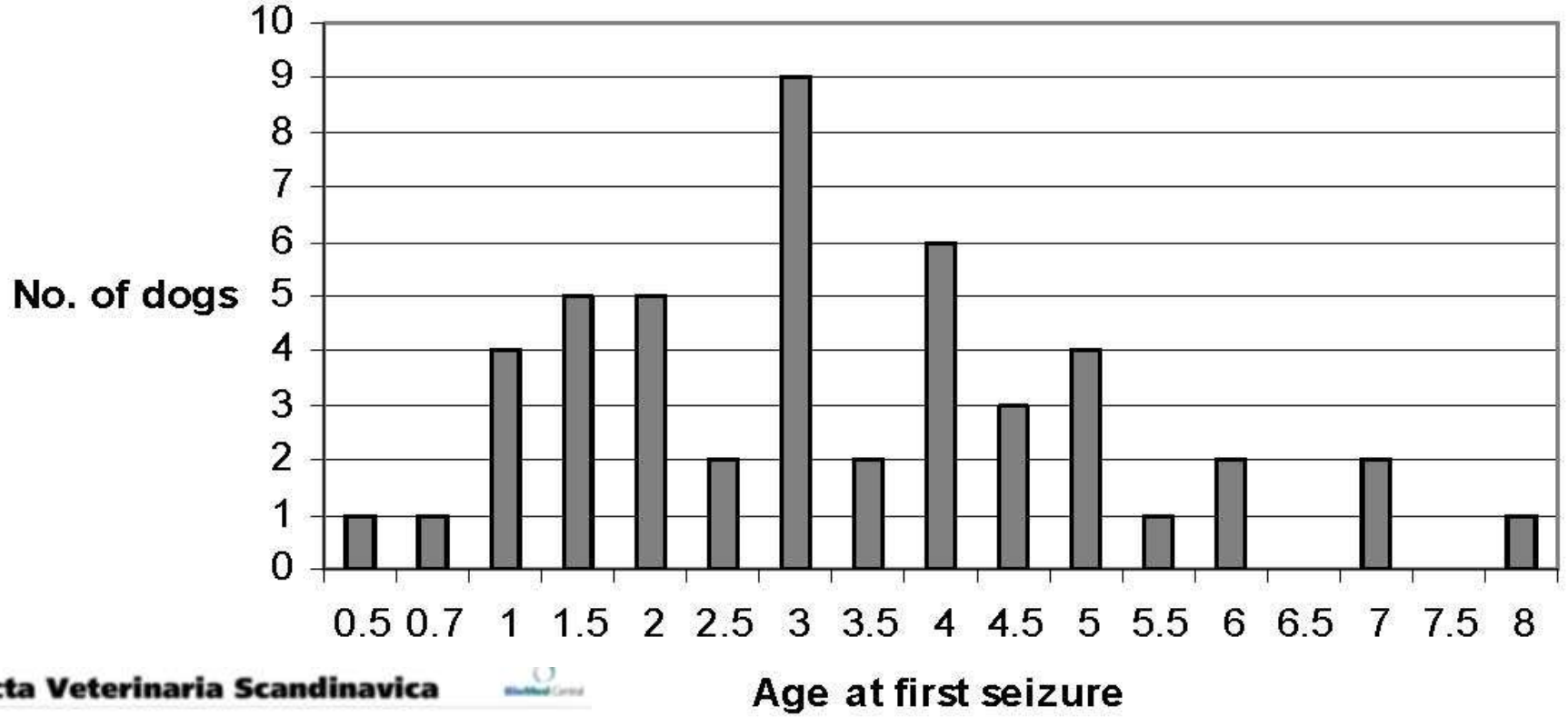
1 in 5 !

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)



Acta Veterinaria Scandinavica

Research

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Prevalence and characteristics of epilepsy in the Belgian shepherd variants Groenendael and Tervueren born in Denmark 1995–2004

Mette Berendt*[1], Christina Hedal Gulløv[1], Stine Louise Krogh Christensen[1], Hulda Gudmundsdottir[1], Hanne Gredal[1], Merete Fredholm[2] and Lis Alban[3]

Vizsla

- No significant **gender predisposition**
  - males slightly overrepresented (59%)
- **median age seizure onset 3y**

Complex inherited disorders

Avoid Matador breeding (popular sire syndrome)

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- 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??

Thank you for listening!

Any questions?