

Lafora's dx and Epilepsy



Scope of Lecture

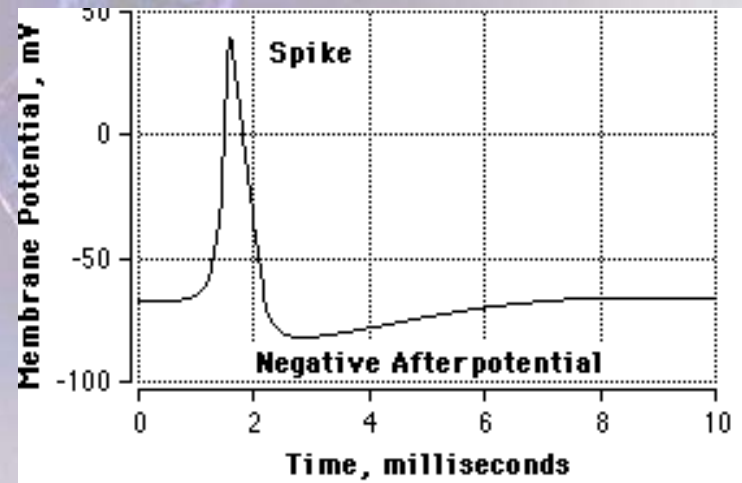
- What is a seizure?
- Idiopathic epilepsy vs Lafora's disease
- What is Lafora's disease?
- Genetics of Lafora's disease
- Preventing Lafora's disease
- Genetics of Idiopathic epilepsy
- Preventing idiopathic epilepsy

What is a seizure?

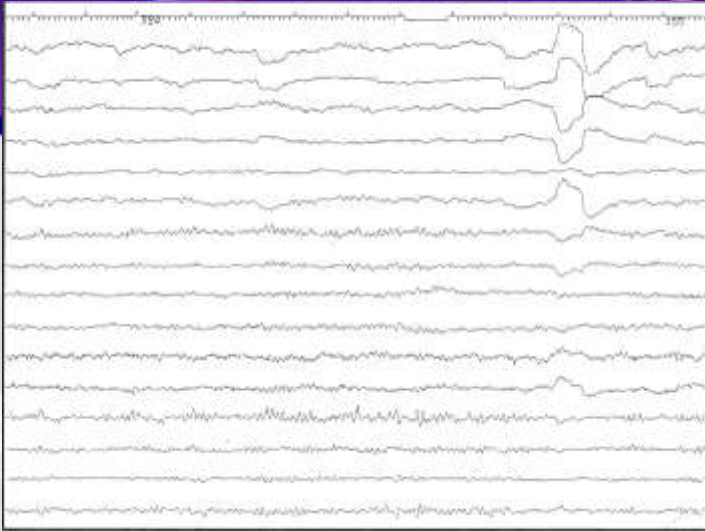
Abnormal brain electrical activity

Sudden episodic transient neurological signs

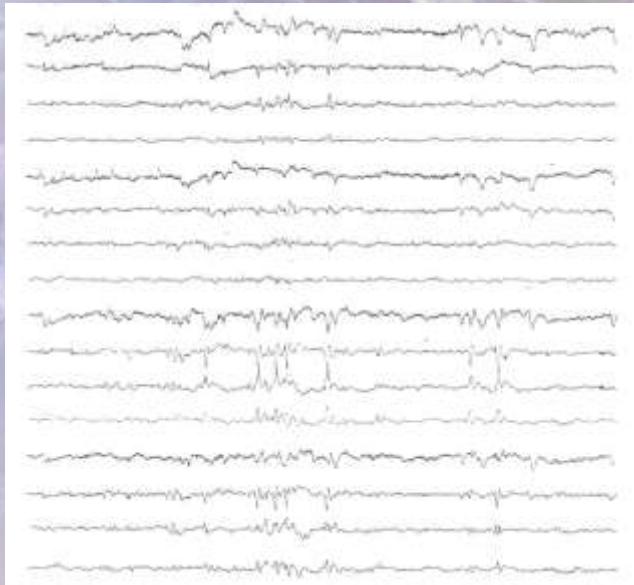
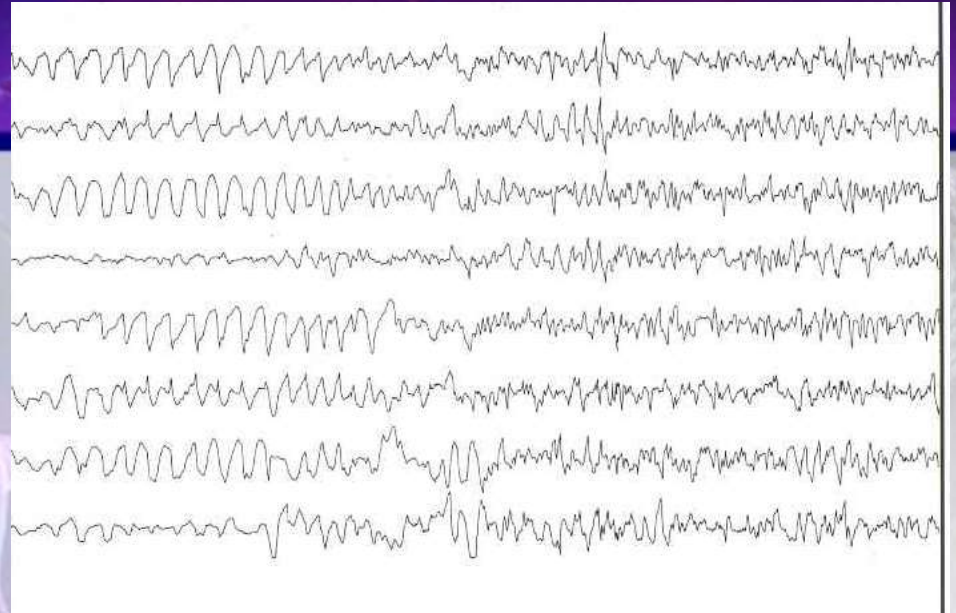
- Involuntary muscle movements
- Sensory disturbances
- Altered consciousness



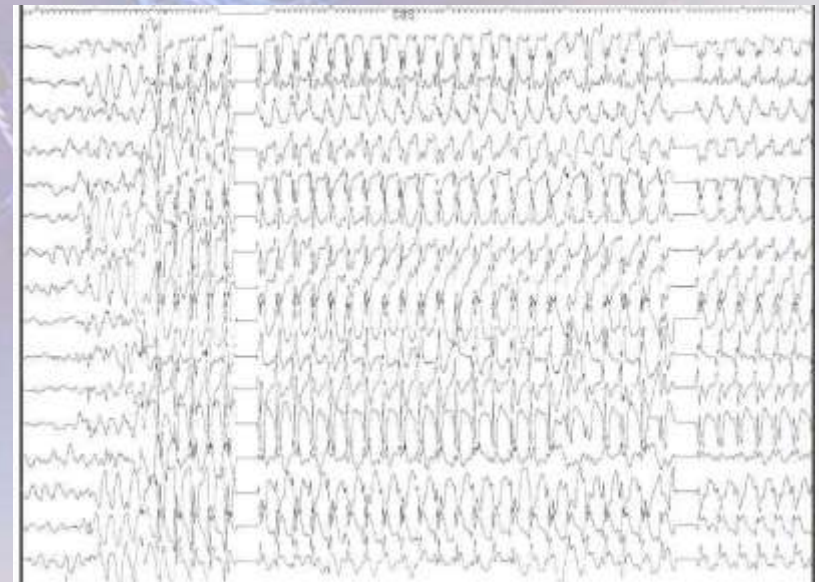
Normal EEG



Generalised tonic clonic



Focal seizure



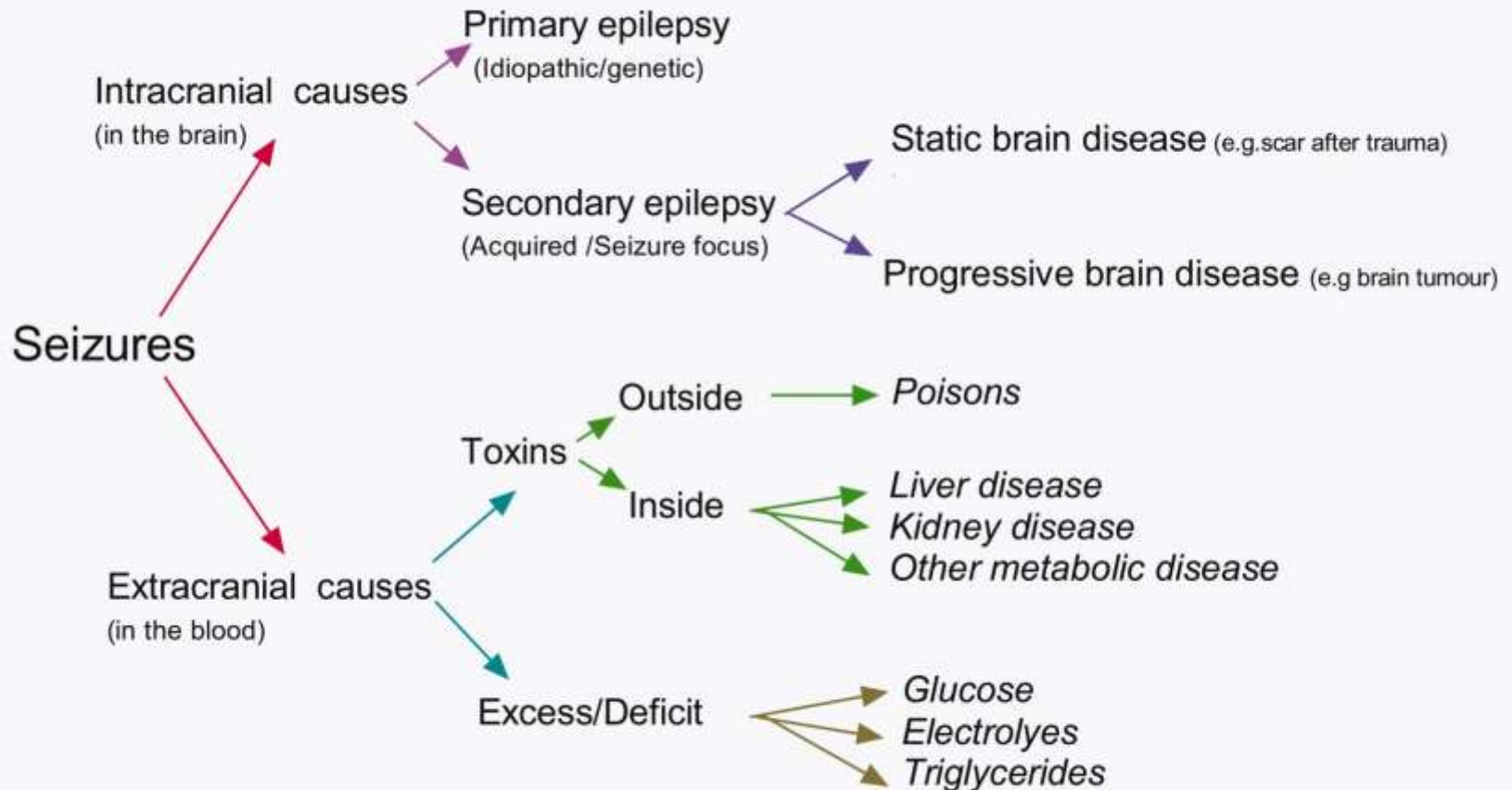
Petit mal (3 per sec spike wave)

What is a seizure?



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Causes of seizures



Idiopathic / Inherited epilepsy

- Increased prevalence in Mini Longs?



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
 - Breed epilepsy prevalence greater than 1-2% suggests inherited tendency
 - Dachshund 1.2% ?
 - **Dachs-Life May 2012: Page 24**
 - **17 dogs – 12 / 17 Mini long**

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

Dachshund 18/1260

(1.4% epileptic dog population)

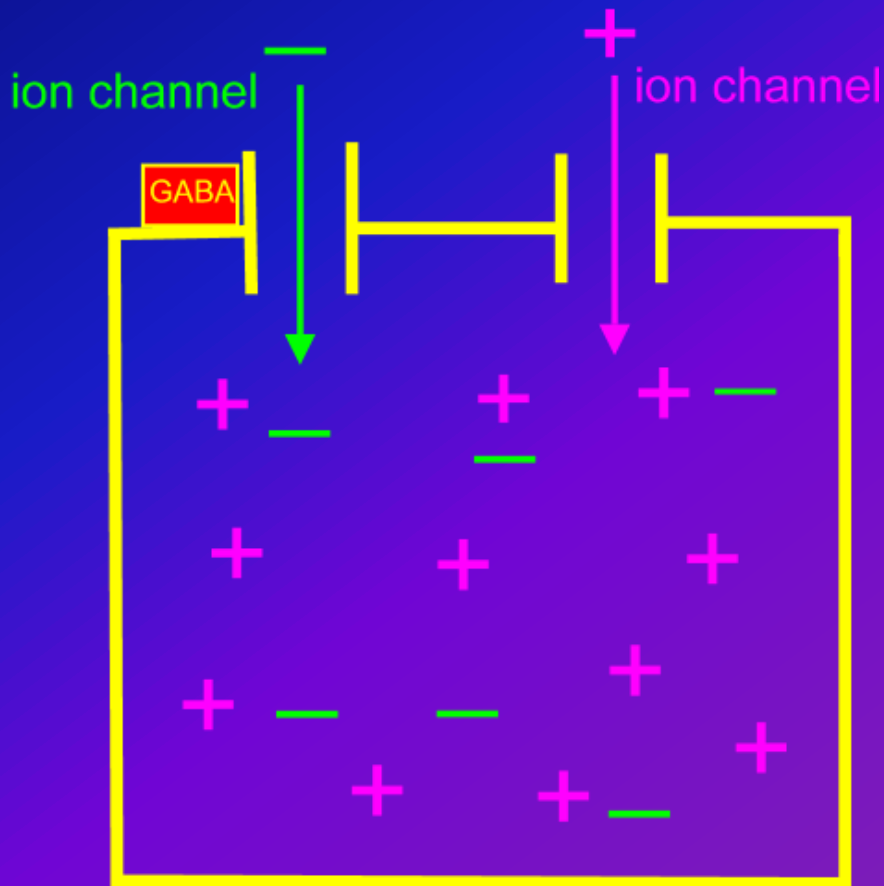
TABLE 1: Breed distribution of a cohort of 1260 dogs with epilepsy

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*†	250 (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)		

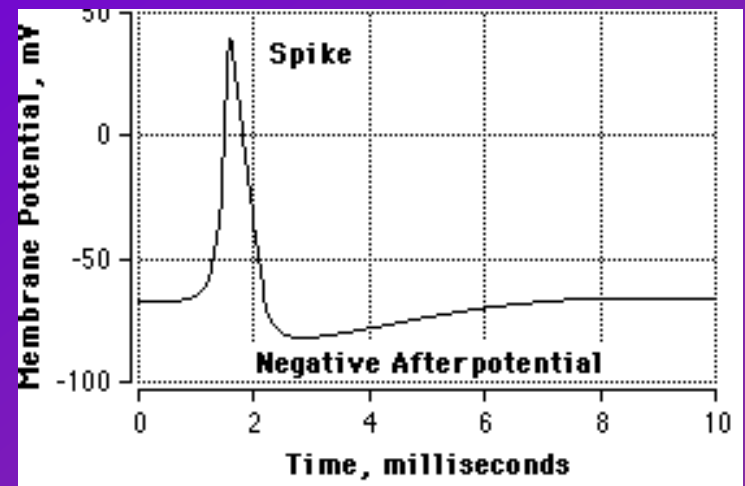
* Top 14 breeds accounting for more than 75 per cent of the epileptic cohort

† Top five breeds accounting for more than 50 per cent of the epileptic cohort

What is idiopathic / inherited epilepsy? Ion channel disorders?



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



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

Lafora's disease

BBC NEWS **LIVE** BBC NEWS CHANNEL

Last Updated: Friday, 7 January 2005, 10:16 GMT
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Epilepsy gene identified in dogs

By Jonathan Amos
BBC News science reporter

Scientists have identified a faulty gene that causes epilepsy in dogs.

The finding has allowed the researchers to develop a test that could soon help owners breed out the disease.

But the discovery should also aid the quest to understand the more severe human form of the condition, Lafora disease, and other similar afflictions.

The latest development, reported in Science magazine, is an example of how the human and dog genome projects are expected to benefit both species.

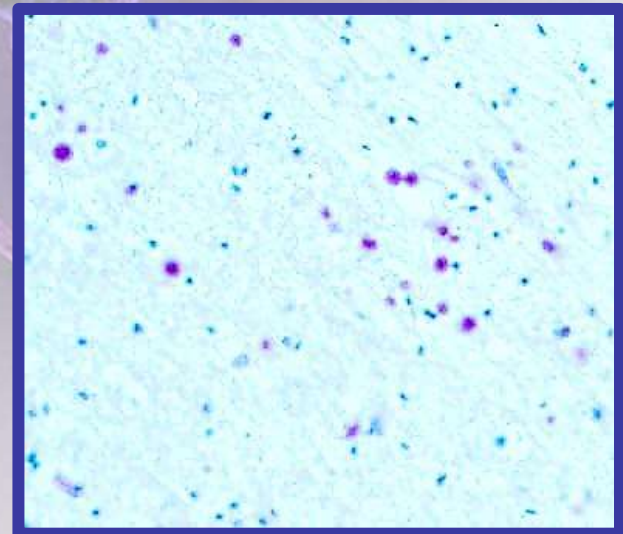
Researchers are comparing and contrasting the "life codes" of the two mammals with other animals to track down the genetic causes of ill-health.



Doggy sunglasses can help control epilepsy

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Lafora's disease - dog

Early

- Myoclonus (jerks)
 - Photosensitive
 - Sudden movement / noise
 - manifestation of cortical irritability
- Seizures

Late

- Panic attacks
 - visual hallucinations?
- Dementia
- Incontinence
- Blindness
- Deafness
- Walking difficulty
 - Stiffness

Lafora's disease - humans

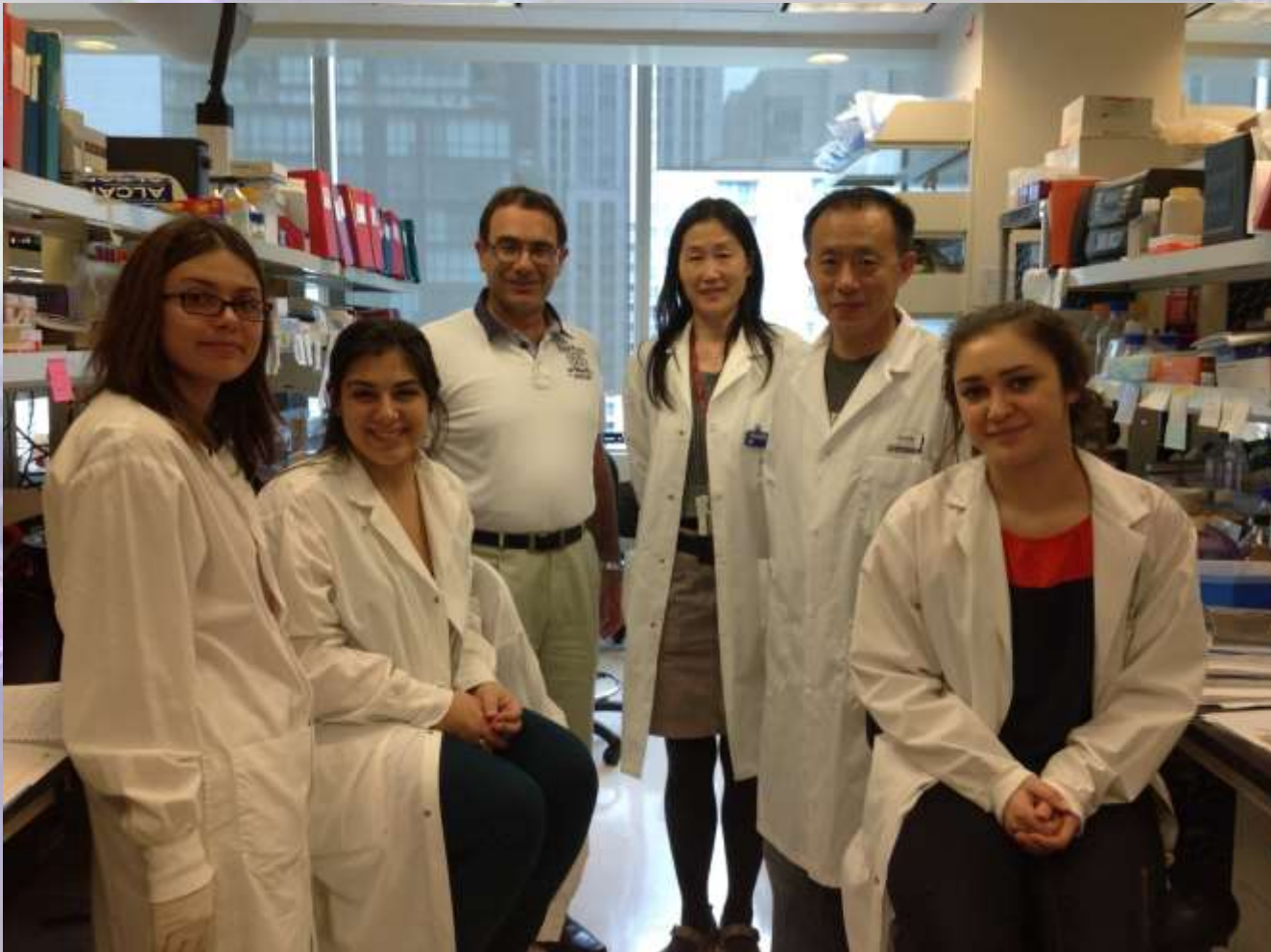
Initial

- Myoclonus
- Seizures
 - myoclonic
 - occipital
 - transient blindness
 - visual hallucinations
 - photoconvulsion
- Tonic clonic
- atypical absence
- atonic
- complex partial

Progressive

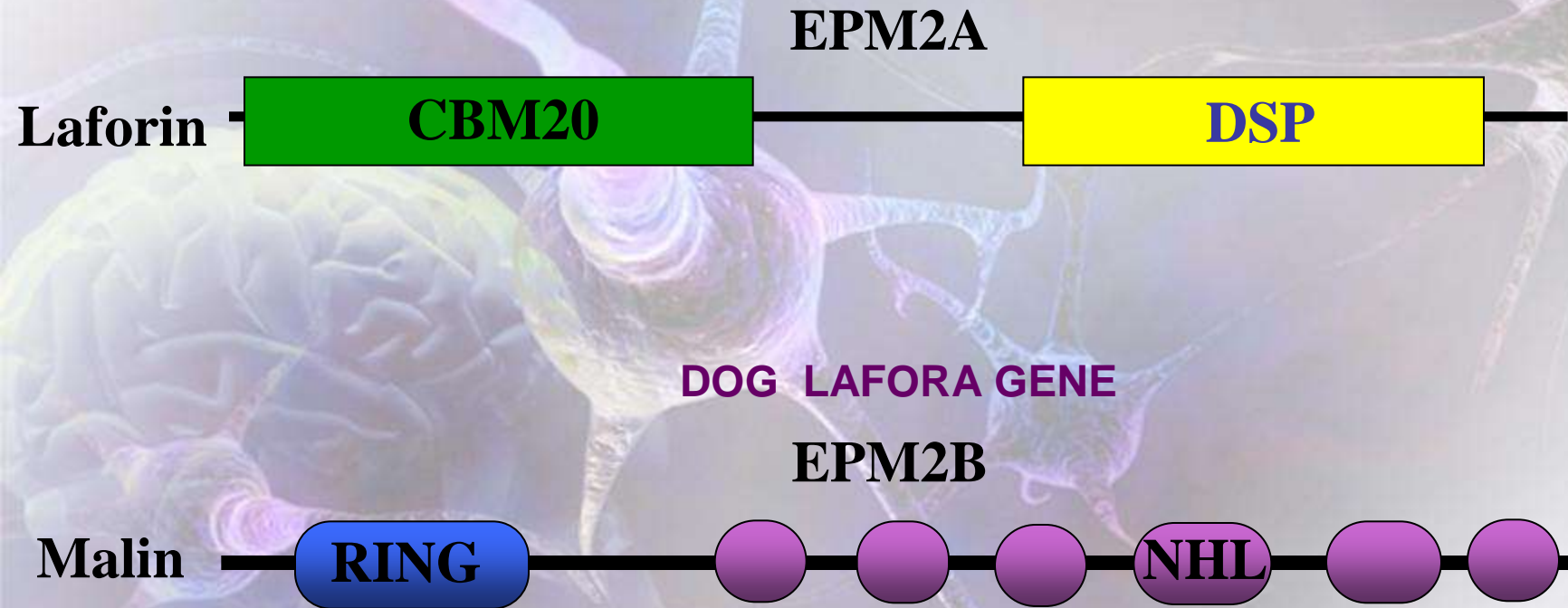
- Cognitive decline
→ → dementia
- Walking difficulty
wobbly → → spastic
- Emotional disturbance and confusion
- Die w/in 10 years
Status epilepticus and complications (e.g. pneumonia)

Berge Minassian Research Lab “Sick Kids” Hospital Toronto



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Lafora disease genes



Deficiency of Malin results in accumulation of malformed glycogen (lafora bodies) in the brain

Acknowledgement - Berge Minassian

Management

- High protein, low simple carbohydrate diet
 - Decrease glycogen?
- Myoclonus
 - Levetiracetum
 - Avoidance triggers
- Seizures
 - Phenobarbital
 - Bromide
 - Zonisamide



Alfie

Message from Berge (23/1/14)

- “we are making really huge progress towards therapies, these would be viral vector based or small molecule. Nothing yet ready for dogs, though we are treating mice”



Chelsea's Hope

Lafora Children Research Fund

Creating Awareness • Connecting Families
Funding Research • Maintaining Hope



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Genetics of epilepsy

Inherited CNS disease

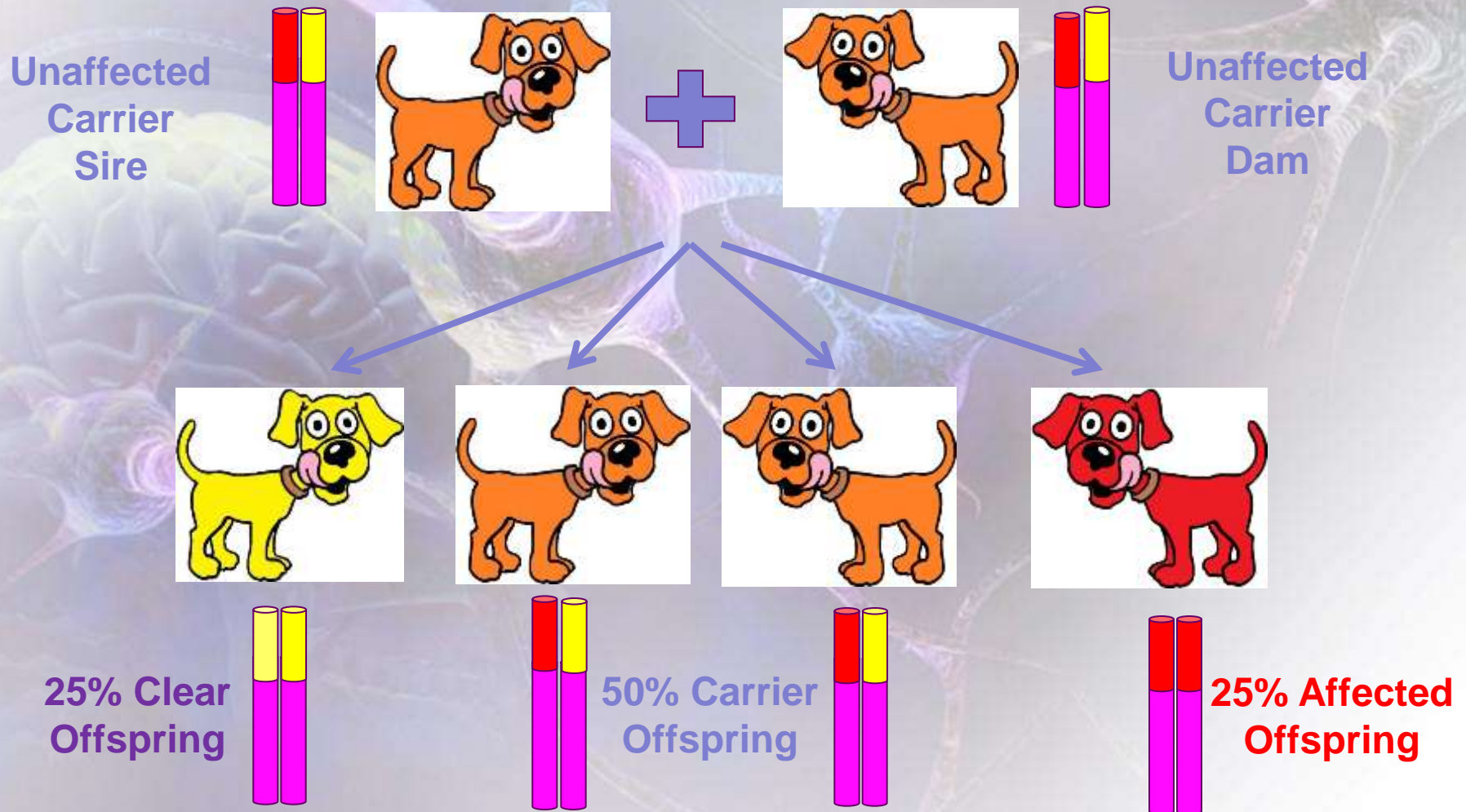
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- Simple (single gene)
 - e.g. lafora's
- Complex
 - e.g. idiopathic epilepsy
- Susceptibility to immune mediated disease
 - e.g. Pug encephalitis
- Inherited susceptibility to neoplasia
 - e.g. brain tumour Boxer dogs



Laforas - Single gene disorder

Simple autosomal recessive



“no brainer” questions

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Should we breed out Lafora's?

Yes!

- Simple and accurate DNA test
- Should be a long term project
- Sensible breeding decisions will avoid “throwing the baby out with the bathwater”
- Pretending its not a problem doesn't make it go away
- Breeders have ultimate responsibility for the health and welfare of their breed

“no brainer” questions

But Lafora's isn't a problem for the breed?

- WHDC's screening programme ~ 10% “affected” MWHDS.
- 40% UK MWHDS could be carriers
- “late onset” disease (5-13y) - dogs have been bred before displaying signs

“no brainer” questions

- The test is too expensive!
 - £150 (subsidised)
 - Cost of attending Ch Show - £100
 - Cost of reasonable (non-Ch) Stud - £400
- I have never seen this as a problem in my lines
 - I don't need to test!
 - Great! the breed needs **known** disease free dogs!
 - Great! you are fortunate to be confident about the results

“no brainer” questions

Lafora's isn't a big problem for the dog?

Lafora's affects old dogs at the end of life?

- Age of onset Laforas ~ 7 years
- Age of death Dachshund ~ 12y7m
 - Purebred Dog Health Survey for Dachshunds (UK Kennel Club)
- 45% of life (or more) is spent with debilitating jerking, seizures, confusion, anxiety, possible hallucinations, difficulty walking and blindness.
- Do you really think that is OK?



Quotes from owners (Lafora dogs survey)

- “We have seldom seen anything in our mini wires more upsetting - both for us and the dog.”
- “The impact of Lafora is enormous, both for our dogs (2 with the disease) and ourselves. We have had to adopt a different way of living trying at all times to make adjustments that will reduce the Lafora symptoms as much as possible. We also have to plan any outings or holidays meticulously to ensure the welfare of the dogs.”

More difficult questions

My dog is a carrier should I breed?

Yes!!

- MW Breed Average COI is 11%
 - Half sibling mating COI is 12.5%
- your dog has valuable and vital DNA
- **Must to mated to DNA tested normal**
 - Some / all offspring may be carriers
 - All offspring must be tested
 - All carriers must be mated to DNA tested normal

More difficult questions

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My dog is affected should I breed?

Perhaps?

- If important to maintain gene pool
 - your dog has valuable and vital DNA
 - Group decision made on other factors e.g. COI
- No evidence (yet) that breeding is detrimental to Lafora dog's health
- Must to mated to DNA tested normal
- All offspring will be carriers
 - Must to mated to DNA tested normal

More difficult questions

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Is there a human reason for not testing?

- **Its better not to know !**

- The results are published
- Reputation is at risk
- Risk of lost income from valuable stud



No-one has perfect DNA!

- A breed with COI of 11% cannot afford to stigmatise dogs or breeders with affected or carrier dogs
- Fingers of blame??
 - should not point at breeders that test and are unfortunate enough to have affected / carrier dogs
 - should point at those who don't test and don't help to improve the health of the breed.



Perfect DNA?????



Genetics of Idiopathic epilepsy

The challenge of finding the genes in a complex disorder

Heritability of epilepsy

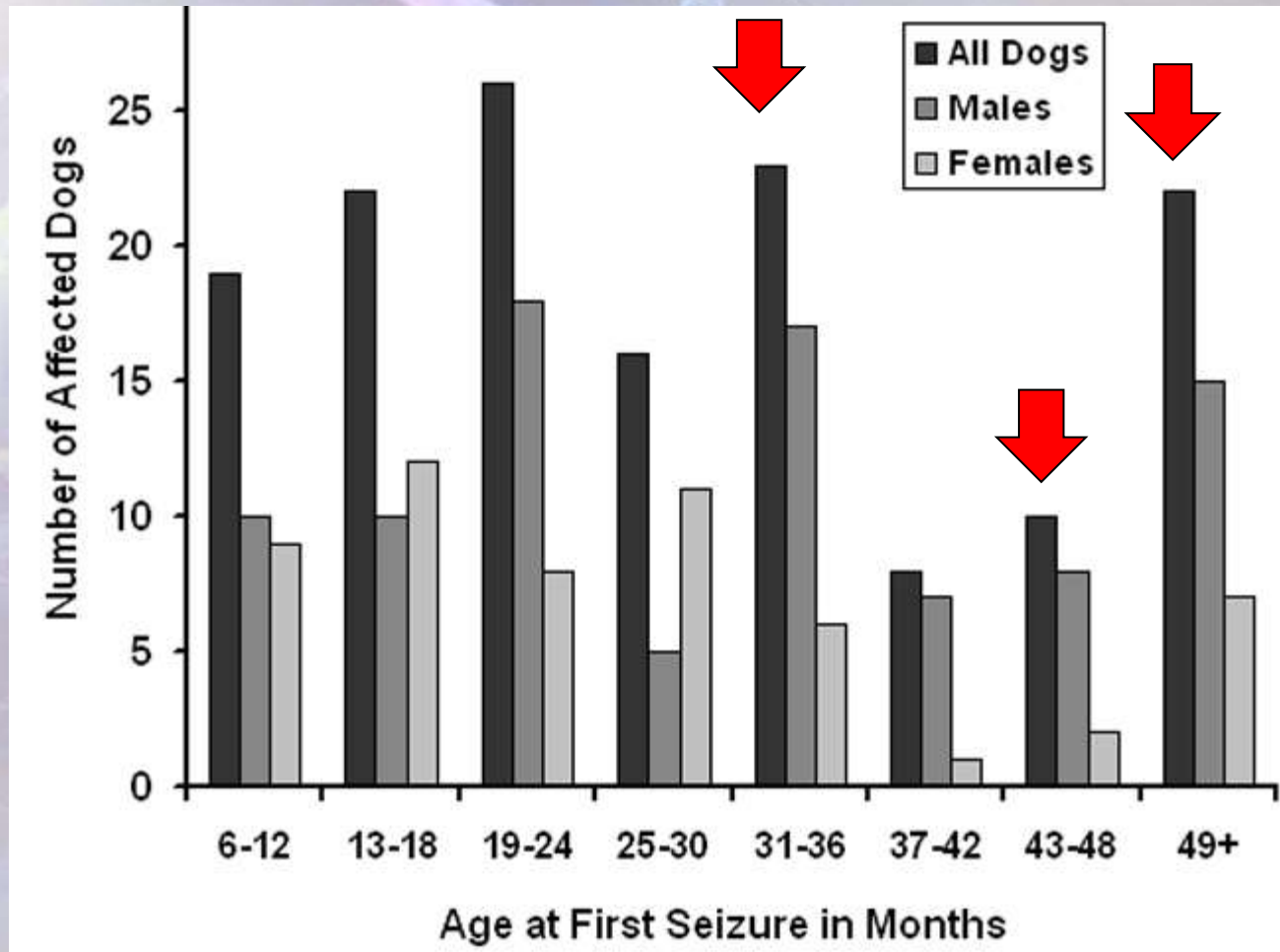
- Most epileptic dogs do not have epileptic parents and epilepsy can skip generations
 - Autosomal recessive
 - Unaffected dogs may be carriers
- Often high e.g. Irish Wolfhounds = 0.87
 - if one knew what to select for it could be “bred out”
 - Expression of disease may be influenced by other as yet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

Inherited epilepsy – challenge of “finding genes” for complex disorder

- More than one gene
- May be late or variable onset
- Diagnostic test may expensive and/or inconclusive
- Effect of environment / other factors
 - Sex / neuter status
 - Diet
 - Weight
 - Exercise
 - Epigenetics
 - non-genetic factors (e.g. [DNA methylation](#)) causing the organism's genes to behave (or "express themselves") differently
 - In times of environmental stress certain genes get turned on / off and this can be passed down to offspring and offspring's offspring
- Difficulty of finding good controls for genetic studies

Age of Onset of Epilepsy

Irish Wolfhounds



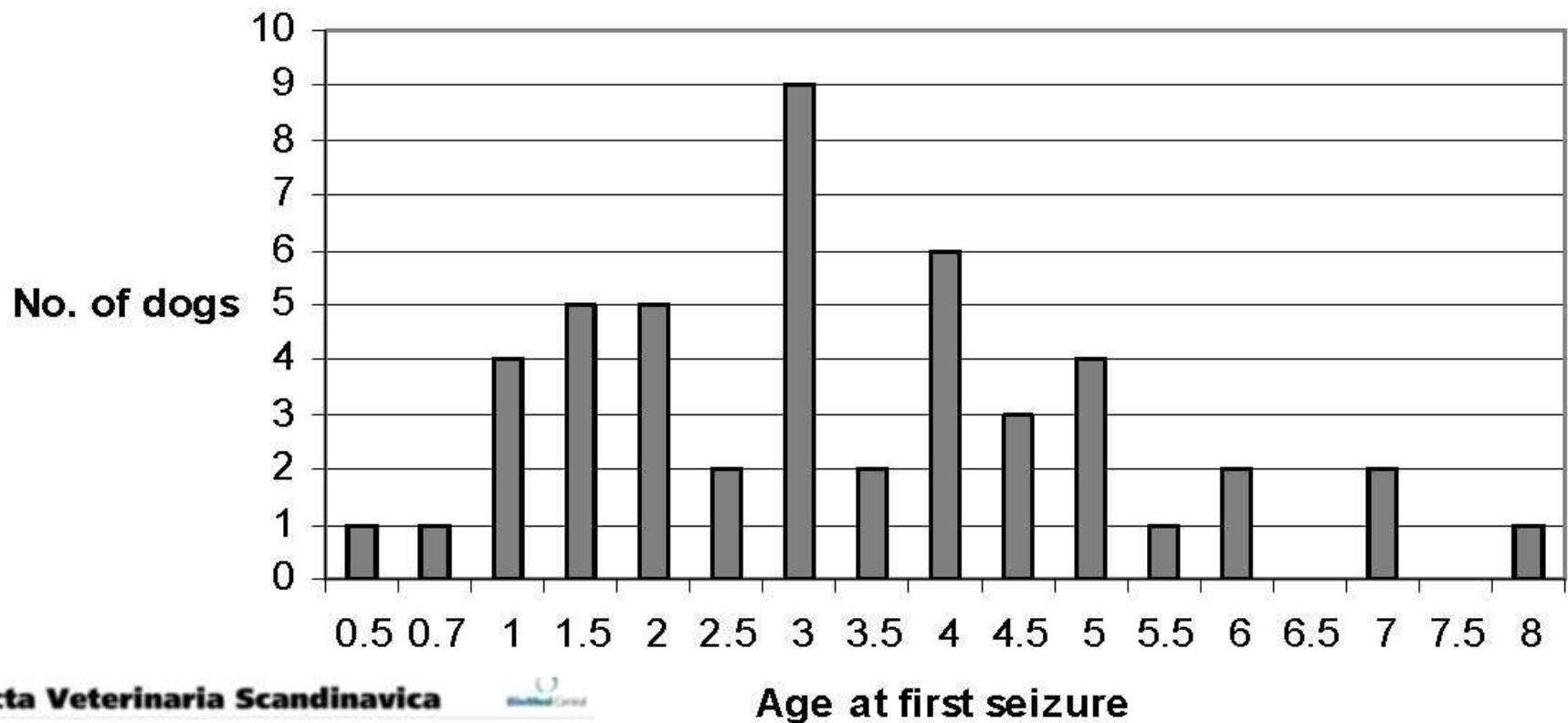
1 in 5 !

**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
Prevalence and characteristics of epilepsy in the Belgian shepherd variants Groenendael and Tervueren born in Denmark 1995–2004
Mette Berendt¹, Christina Heddal Gullov¹, Stine Louise Krogh Christensen¹, Hulda Gudmundsdottir¹, Hanne Gredal¹, Merete Fredholm² and Lis Alban³

Open Access

Finding generalised IE genes so how is that going?

- Lupa <http://www.eurolupa.org/>
 - Dog genetics to understand human diseases
 - Collaboration of 20 veterinary schools from 12 European countries
 - Large DNA collections from many breeds
 - Investigation many disease including IE
 - Lagotto Romagnola (Finland – Hannes Lohi)
 - Finnish Spitz (Finland – Hannes Lohi)
 - Border Collie (AHT, UK)
 - Norwich Terrier (AHT, UK)



Finding generalised IE genes so is there any progress?

Belgian Shepherds

- Novel Idiopathic Epilepsy Locus identified
 - Small region (1MB) of chromosome
 - Contains 12 genes
 - No known epilepsy genes
 - None encode ion channels
 - one candidate gene ADAM23 most likely
 - interacts known epilepsy proteins LGI1 and LGI2
 - Having 2 copies of SNP variation increases risk epilepsy
- Still need to identify mutation
- ? DNA test
- Life span not affected



Picture thanks to Tim Rose Dog's Today

OPEN ACCESS Freely available online

PLoS one

Identification of a Novel Idiopathic Epilepsy Locus in Belgian Shepherd Dogs

Eija H. Seppälä^{1,2,3}, Lotta L. E. Koskinen^{1,2,3}, Christina H. Gulløv⁴, Päivi Jokinen^{1,2,3}, Peter Karliskov-Mortensen⁵, Luciana Bergamasco⁶, Izabella Baranowska Körberg⁷, Sigita Cizinauskas⁸, Anita M. Oberbauer⁹, Mette Berendt⁴, Merete Fredholm⁵, Hannes Lohi^{1,2,3*}

Influence of other genetic factors

Why are some epileptic dogs refractory to AED?

- ~ 1/3 epileptic dogs & humans refractory to drugs
- unresponsive to multiple drugs with a wide range of mechanistic actions
- If seizures haven't controlled on 2 drugs then much less likely to ever get good control
- Genetic or disease-related alteration in drug target?
 - decreased sensitivity to treatment.
- Overexpression drug transport proteins?
 - Limits penetration of drugs into the brain
 - e.g. P-glycoprotein (ABCB1 gene)



P-glycoprotein (ABCB1 gene) in Border Collies

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- Mutation noncoding, promoter region
- associated resistance to phenobarbital
- affect expression of ABCB1 gene?
- influence the response to drugs?



JVIM 2011;25:484-9. Alves L et al
Polymorphisms in the ABCB1 gene in phenobarbital responsive
and resistant idiopathic epileptic Border Collies.

Summary – genetics and epilepsy

- Genetics plays an important part
 - 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
 - Better understand & treat human epilepsy



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 work together

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??



Appendix

Other influences

Neutering

- Advisable to spay epileptic bitches?
 - Oestrogen lowers seizure threshold
 - study 37% intact bitches had 1st sz when in heat
 - Frequency seizures can increase during oestrus
 - Progesterone increases seizure threshold
- Castration doesn't influence seizure frequency?
 - Neuter to avoid breeding?
 - study found that entire dogs with I.E. 1.9x more likely to have cluster seizures

Stress triggers?

The following have not been shown to influence seizures

Housing

Season

Days of the week

Public holidays

Feeding habits

Lunar cycle

Weather

- Occasionally an individual dog will have obvious repeatable trigger factor e.g. exercise
- When seizure due there may be a stress triggers
 - e.g. sudden noise, waking the animal from sleep.
 - in interictal period the same trigger has no effect

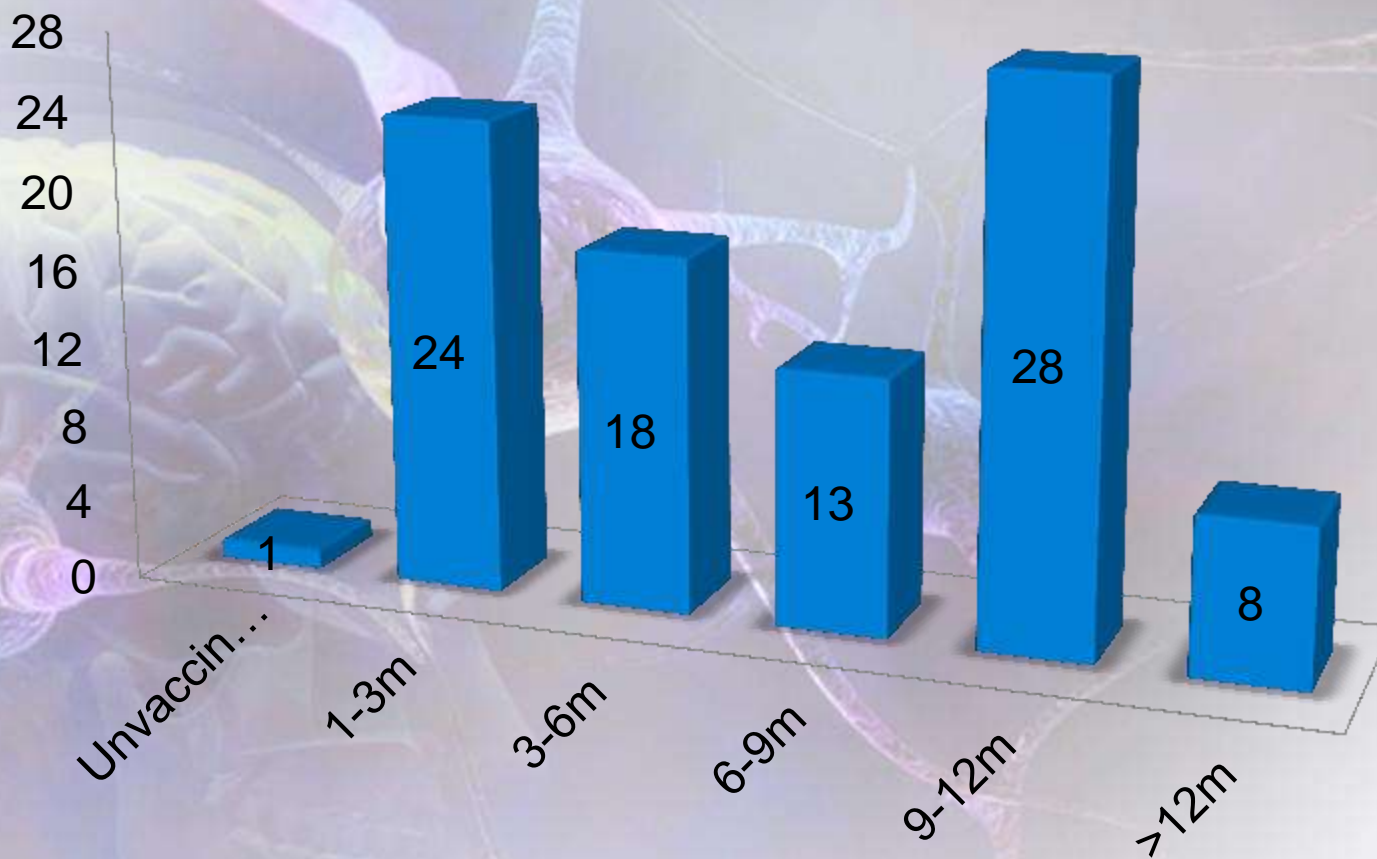
Diet

- Low protein diet?
 - affects monoamine neurotransmitters
 - no scientific investigation
 - few dogs appear to respond to diet change
- Dietary intolerance?
 - hypoallergenic / hydrolysed if signs food intolerance e.g. skin or gastrointestinal disease ?
- Ketogenic diet? (high fat, low carbohydrate)
 - Useful refractory epilepsy humans esp children
 - Recent trials with specially manufactured food
 - no reduction in seizure compared to control diet
 - number of seizures did decrease in both groups suggesting that dietary consistency may help control seizures.

Vaccination

- Do more epileptic dogs have 1st seizure within 3m of vaccination?
- Can vaccination trigger seizures?
 - small number of dogs do have seizures associated with vaccination
 - chance
 - stress of veterinary visit
 - immunological effects of vaccination (pyrexia?)

1st seizure - time after vaccination



No significant difference
between vaccinated groups

■ Number of dogs