IWDBA Breeders Workshop 2023

Neurology

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Epilepsy genes

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Canine idiopathic epilepsy

- Diagnosis of exclusion
- Relatively few identified epilepsy genes.
- Phenotypes differ between breeds and geographically distinct populations.
- Mainstay of treatment AED’s.
- For the majority of general practice dogs, idiopathic epilepsy diagnosed based on 2 seizures and no abnormalities on blood panel.

Update on human epilepsy

- Range of phenotypes
- Advances in genetic technology has resulted in identification of causes of previously classified “idiopathic epilepsy”
- 100’s epilepsy genes identified.
- Development of precision medicine – medications other than AEDs can be useful.

Data required for phenotype characterisation

- Age of onset
- Seizure semiology (subjective and objective symptoms)
- Seizure frequency
- Triggering factors/ pattern of occurrence
- History of related individuals incl. spontaneous abortions or infantile deaths.
- Behaviour abnormalities – ADHD, ASD
- Motor and language skills.
- EEG and MRI

Image courtesy: **From genetic testing to precision medicine.** Pasquale Striano et Berge Minassian. ***Neurotherapeutics (2020) 17:609-615.***

Table 1 Examples of precision medicine applied to epilepsy

Epilepsy syndrome (# OMIM)	Gene(s)	Protein function	Possible targeted treatments
Pyridoxin-dependent epilepsy (#266100)	*ALDH7A1*	Aldehyde dehydrogenase	Pyridoxine (B6 vitamin)
Focal epilepsy with speech disorder, with/without mental retardation (#245570)/EIEE 27 (# 616139)	*GRIN2A, GRIN2B*	NMDAR subunits	NMDAR antagonists (memantine) and dextromethorphan, potentially useful (GOF variants)
EIEE 32 (# 616366)	*KCNA2*	Voltage-gated potassium channel	Potential efficacy of 4-aminopyridine (4-AP, Kv1 channels inhibitor) for GOF variants
EIEE 7 (#613720); BFNS1 (#121200)	*KCNQ2*	Voltage-gated potassium channel	Potassium channel openers (Retigabine and Ezogabine for LOF variants), potential efficacy of sodium channel blockers (CBZ)
EIEE 14 (#614959); Nocturnal frontal lobe epilepsy (#615005)	*KCNT1*	Sodium-activated potassium channel	Potassium channel openers (Quinidine for GOF variants)
PNP oxidase deficiency (#610090)	*PNPO*	PNP oxidase	Pyridoxal-5-phosphate
Familial infantile convulsions with paroxysmal choreoatetosis (#602066); BFIS 2 (#605751)	*PRRT2*	Coregulator of synaptic transmission	sodium channel blocker (carbamazepine)
Dravet syndrome (#607208)	*SCN1A*	Voltage-gated sodium channel subunit	Avoid sodium channel blockers (carbamazepine, phenytoin)
EIEE 11 (#613721)/BFIS 3 (#607745)	*SCN2A*	Voltage-gated sodium channel subunit	Sodium channel blockers for GOF variants; avoid sodium channel blockers for LOF variants
EIEE 13 (#614558); BFIS 5 (#617080)	*SCN8A*	Voltage-gated sodium channel subunit	Favor sodium channel blockers for GOF variants
GLUT1 deficiency (#606777; #612126)	*SLC2A1*	Glucose transporter	Ketogenic diet
FCD type II (#607341)	*mTOR, TSC1, TSC2*	mTOR pathway effectors/regulators	Everolimus and other mTOR inhibitors

BFIS (benign familial infantile seizures); *BFNS* (benign familial neonatal seizures); *CBZ* (carbamazepine); *EIEE* (early infantile epileptic encephalopathy); *FCD* (focal cortical dysplasia); *GOF* (gain-of-function); *LOF* (loss-of-function); *LTG* (lamotrigine); *NMDAR* (*N*-methyl-D-aspartate receptor); *PHT* (phenytoin); *PNP* (pyridoxine 5-prime-phosphate)

Benign Juvenile Epilepsy

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What are juvenile seizures?

- Juvenile seizures are those that occur at a young age of life.
- They generally are self limiting – resolve as the dog matures.
- Synapses in the brain are formed during the last trimester and extend in the first few weeks of life.
- At around 7 weeks of age (breed dependent) synaptic pruning occurs. Synapses/ connections in the brain that are not used are removed to make the brain work more efficiently.
- Pruning usually complete by around 14 weeks of age.
- Reported in humans and other species.

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Juvenile seizures – Lagotto Romagnolo

Lagotto – Benign Familial Juvenile Epilepsy

- Ave age of onset = 6.3wks.
- Remission by 13 weeks of age.
- Approx 10% will develop epilepsy in adulthood.
- 2007 study of 58 Lagotto puppies (9 related litters)
- Some pups have ataxia or hypermetria between seizures.
- Clinical signs varied among pups and within litters.
- Autosomal recessive. LGI2 gene.

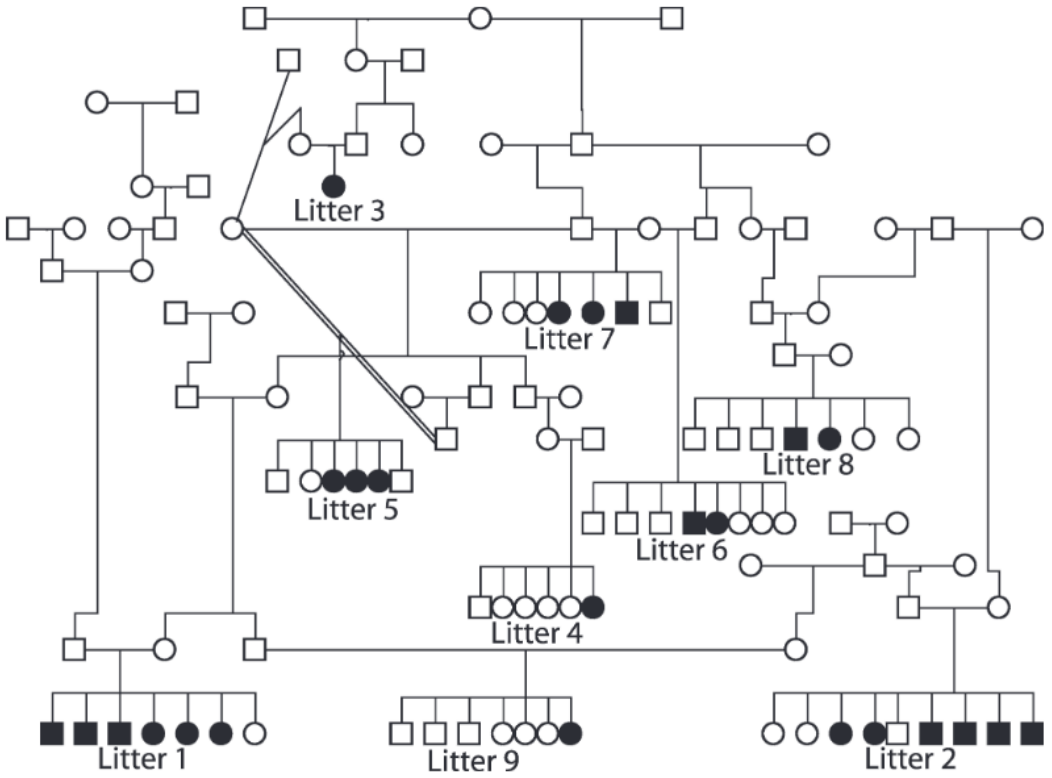
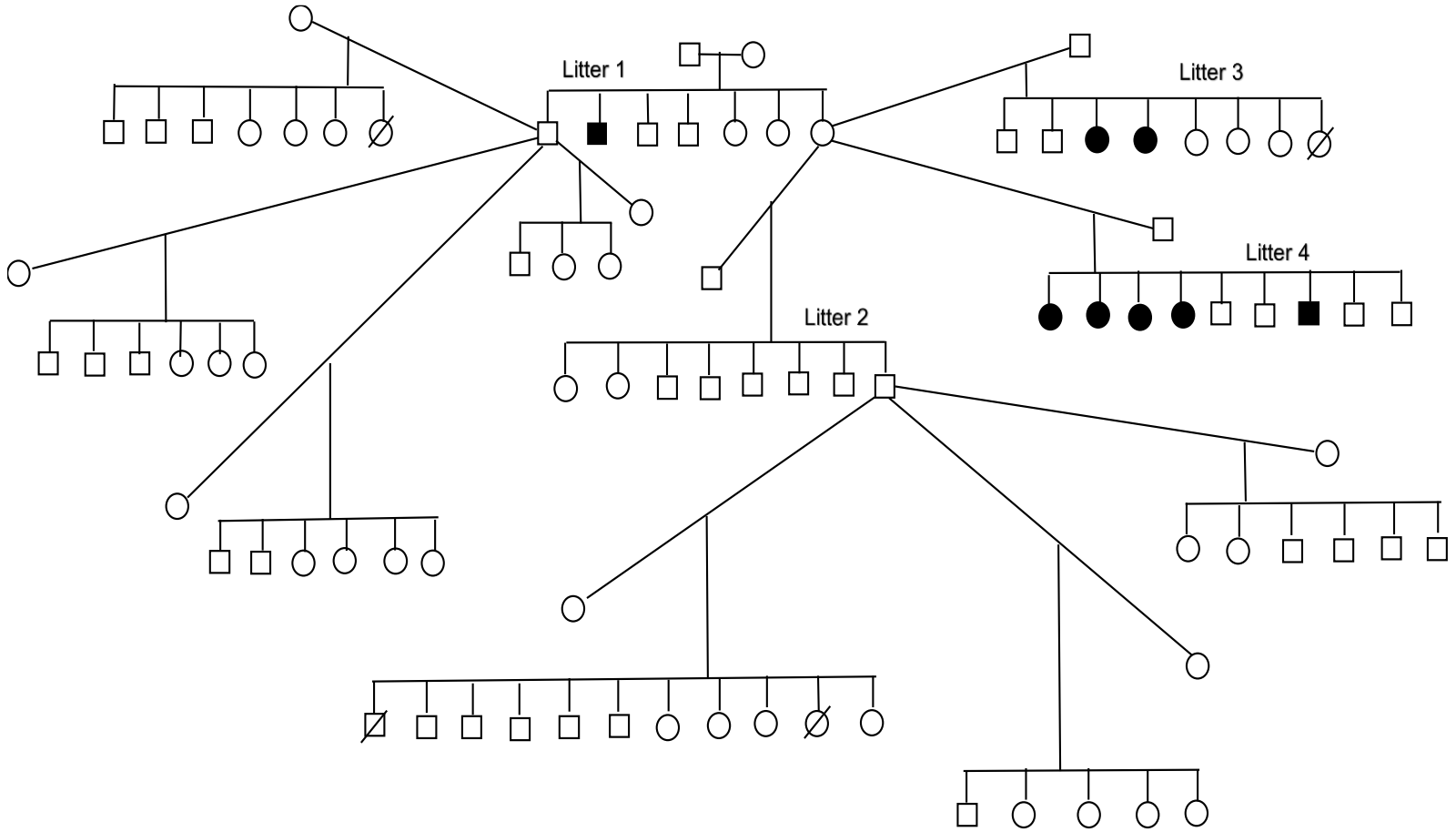


Fig 4. Pedigree of Lagotto Romagnolo puppies with juvenile epilepsy. All 25 affected puppies representing both sexes were born to unaffected parents, consistent with an autosomal recessive mode of inheritance. Square = male; circle = female; shaded symbol = affected dog. In litter 2, the only unaffected male dog is actually a hermaphrodite.

Jokinen, T.S., Metsähonkala, L., Bergamasco, L., Viitmaa, R., Syrjä, P., Lohi, H., Snellman, M., Jeserevics, J. and Cizinauskas, S. (2007), Benign Familial Juvenile Epilepsy in Lagotto Romagnolo Dogs. Journal of Veterinary Internal Medicine, 21: 464-471. https://doi.org/10.1111/j.1939-1676.2007.tb02991.x

Juvenile seizures at GDN



Neuronal Maturation Defect

- Out of 8 affected puppies, one female clinically affected at adulthood.

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Idiopathic Head Tremor Syndrome (IHTS)

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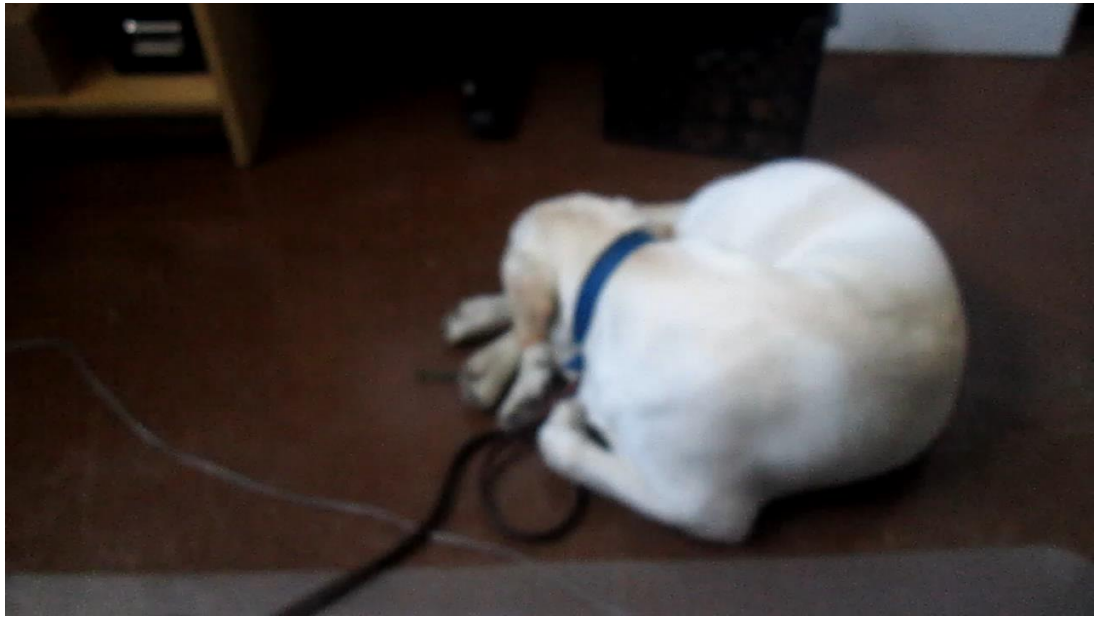
What is Idiopathic head tremor syndrome?

- Benign episodic head tremors in either vertical (“yes”) or horizontal (“no”) pattern. Rotational is uncommon.
- Considered a movement disorder.
- Dogs are conscious during episodes.
- Common sire identified in Dobermanns = genetic basis.
- In a study published in 2015[†].
  - Age of onset ranged from 3 months to 12 years.
  - In 82% of cases, episodes last less than 5 minutes.
  - In 87% of cases, distractions caused the tremor to disappear.

[†]Linda G. Shell, John Berezowski, Mark Rishniw, Belle M. Nibblett, Patrick Kelly, "Clinical and Breed Characteristics of Idiopathic Head Tremor Syndrome in 291 Dogs: A Retrospective Study", *Veterinary Medicine International*, vol. 2015, Article ID 165463, 6 pages, 2015. https://doi.org/10.1155/2015/165463.

Videos of IHTS



Triggers for IHTS

Study 1♯

- Stressful events triggered episodes in dogs: 41% baseline, 54% during study.

Study 2*

- Stressful events triggered episodes in 46.7% of Dobermanns.

Study 3!

- 50% of Bulldogs resolved on own without treatment.
- 7% had stressful events as triggers.

Study 4ˇ

- Discussion regarding stretch receptors in neck correlated to IHTS.
- 67% of cases resolved.

♯Schneider N, Potschka H, Reese S, Wielaender F, Fischer A. Imepitoin for treatment of idiopathic head tremor syndrome in dogs: A randomized, blinded, placebo-controlled study. J Vet Intern Med. 2020 Nov;34(6):2571-2581. doi: 10.1111/jvim.15955. Epub 2020 Nov 7. PMID: 33159484; PMCID: PMC7694850.
*Wolf M, Bruehschwein A, Sauter-Louis C, Sewell A, Fischer A. An inherited episodic head tremor syndrome in Doberman pinscher dogs. Movement disorders 2011 Sept:26(13):2381-2386. https://doi.org/10.1002/mds.23936
!Guevar J, De Decker S, Van Ham L, Fischer A, Volk H. Idiopathic head tremor in English bulldogs. Movement disorders 2014 Feb:29(2):191-194. https://doi.org/10.1002/mds.25767
ˇLinda G. Shell, John Berezowski, Mark Rishniw, Belle M. Nibblett, Patrick Kelly, "Clinical and Breed Characteristics of Idiopathic Head Tremor Syndrome in 291 Dogs: A Retrospective Study", *Veterinary Medicine International*, vol. 2015, Article ID 165463, 6 pages, 2015. https://doi.org/10.1155/2015/165463.

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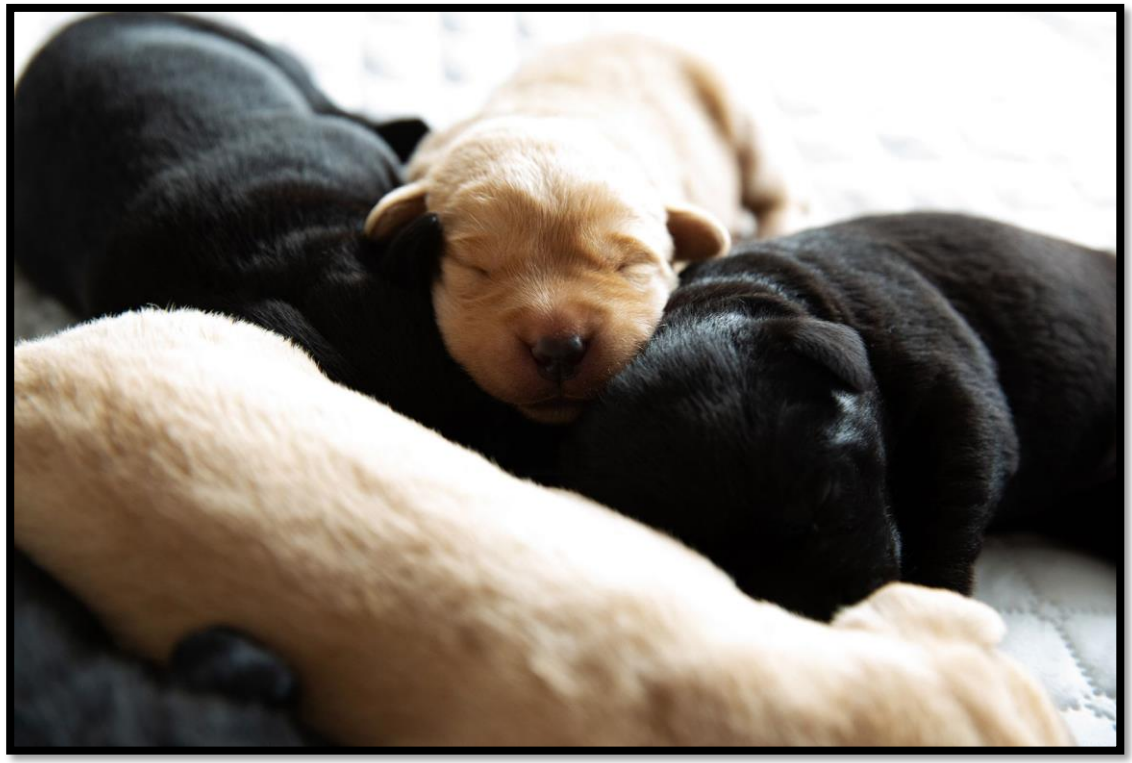
Triggers

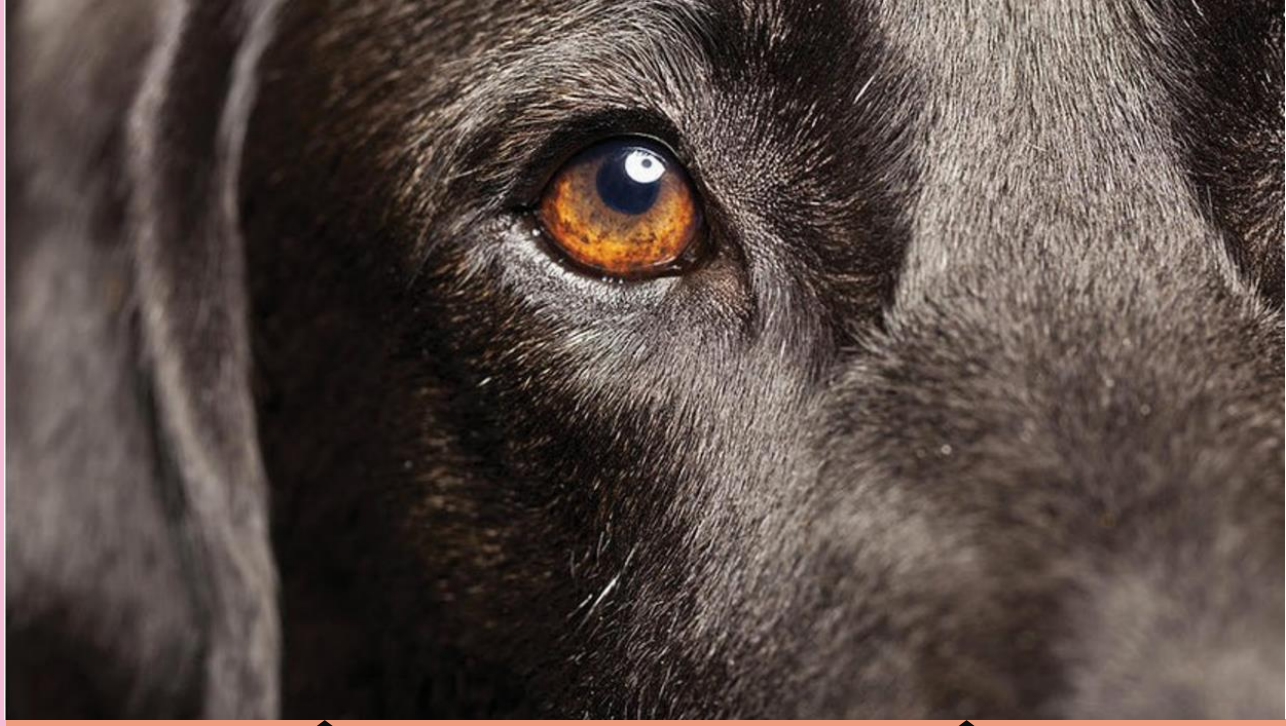
- Taking blood from the jugular – single episode.
- Waking up from anaesthetic (x-rays and ear flush) – single episode.
- Car trip
- Placement with a GD client – repeated episodes.



Outcomes

- Resolution in 93% of cases.
- Most having a single episode.
- Two dogs had episodes over the space of 1-2 weeks before resolution.
- One GD returned as episodes did not resolve.

Thank you



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