

The Genetics of Canine Glaucoma

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The Supervisors

- **Dr Cathryn Mellersh**
 - Head of Canine Genetics, AHT
- **Professor Alison Hardcastle**
 - Professor of Molecular Genetics, IoO, UCL
- **Professor Paul Foster**
 - Professor of Ophthalmic Epidemiology & Glaucoma Studies, IoO, UCL



Funding

- Dogs Trust: £97,000
- Pet Plan: £33,040 (FCR)
- AKC Acorn: £8000 (WSS)
- ECVO: £3960 (FCR)
- BrAVO: £1000 (FCR)
- AHT: £2745 (FCR)
- Breed clubs (WSS, FCR, GR & Leonberger): £12000
- **Total: £157,745**



Decoding glaucoma

For World Glaucoma Week, running 8-14 March, *Dogs Today* is shining a spotlight on the canine side of this devastating disease. Every year in the UK at least 1,500 dogs lose eyes to glaucoma. How can we put a stop to this?

The answer may lie in a certain predisposing factor, goniodysgenesis, which is an inherited abnormality of the eye's drainage angle, and is screened for with a gonioscopy. Now a new six-year study by the Animal Health Trust, funded with £100,000 from Dogs Trust, hopes to identify the mutations responsible for goniodysgenesis and

eradicate them from the gene pools of affected breeds.

AHT vet James Oliver (pictured right) explains, "For those breeds affected by goniodysgenesis, eye screening by gonioscopy is advised before breeding. One problem with this, however, is that goniodysgenesis can be progressive and therefore may be missed if screening is performed in a

young dog. That's why a genetic test would be ideal."

Glaucoma can be a real shock to dog and owner alike. Falcie often aren't aware of the risk, and when it appears, the effects can be instantly life-changing, as owner Barbara Warner discovered with her Golden Retriever, Taffy (above).

A whiz at agility and gundog trials, the seven-year-old was always happy and healthy, so it was a real worry to Barbara when one October evening last year, Taffy suddenly became withdrawn and unsettled, and showed sensitivity to light. Within 24 hours, it was confirmed that Taffy had glaucoma, and just a few days later, the affected eye was removed.

Skinhead

"I had no idea that dogs could get glaucoma or that it could be an inheritable condition in Golden Retrievers," says Barbara. "Taffy is of a very high pedigree; I went through all the normal checks with him for hip and elbow dysplasia, but something like glaucoma never crossed my mind."

"Naturally, I was quite worried at first when I was told Taffy would probably need the eye removed, but James Oliver at the AHT assured me that Taffy could

What is glaucoma?

There are two key types of glaucoma: secondary and primary. Secondary glaucoma occurs following injury, inflammation or cancer of the eye, whereas primary glaucoma is an inherited abnormality of the eye's fluid drainage system. Primary glaucoma can be further categorised as either angle-closure glaucoma (PACG) or open-angle glaucoma.

A dog affected by hereditary glaucoma is very likely to be affected in both eyes, often within six months to two years of the initial diagnosis.

What are the signs?

- Pain. An affected dog may be unsettled, quiet and reluctant to eat. The eye may be closed or the dog might paw at it.
- Blindness. This may not be obvious to the owner, as dogs cope well with vision from the remaining eye.
- Redness of the white of the eye.
- Cloudy appearance at the front of the eye.
- The eye may retreat into its socket, or appear to bulge.
- Dilated pupil.

How can it be prevented?

As an inherited condition, puppy buyers should be aware of the health risks to their chosen breed. Every breed on the aforementioned list should be screened with gonioscopy testing under the BVA/KC/ISDS eye scheme before breeding.

For now the best way to prevent primary glaucoma is to contribute to the research. Dr Cathryn Mellersh (pictured below right), head geneticist at the Kennel Club Genetics Centre at the Animal Health Trust, wants to highlight the owner involvement that was required for the revolutionary glaucoma test for the Petit Basset Griffon Vendéen.

"This would not have been possible without the input from the people who own and breed these dogs," she says. "It is such a sad thing to have to go through as an owner, but they need to tell us about it, and that way some good can come from it."

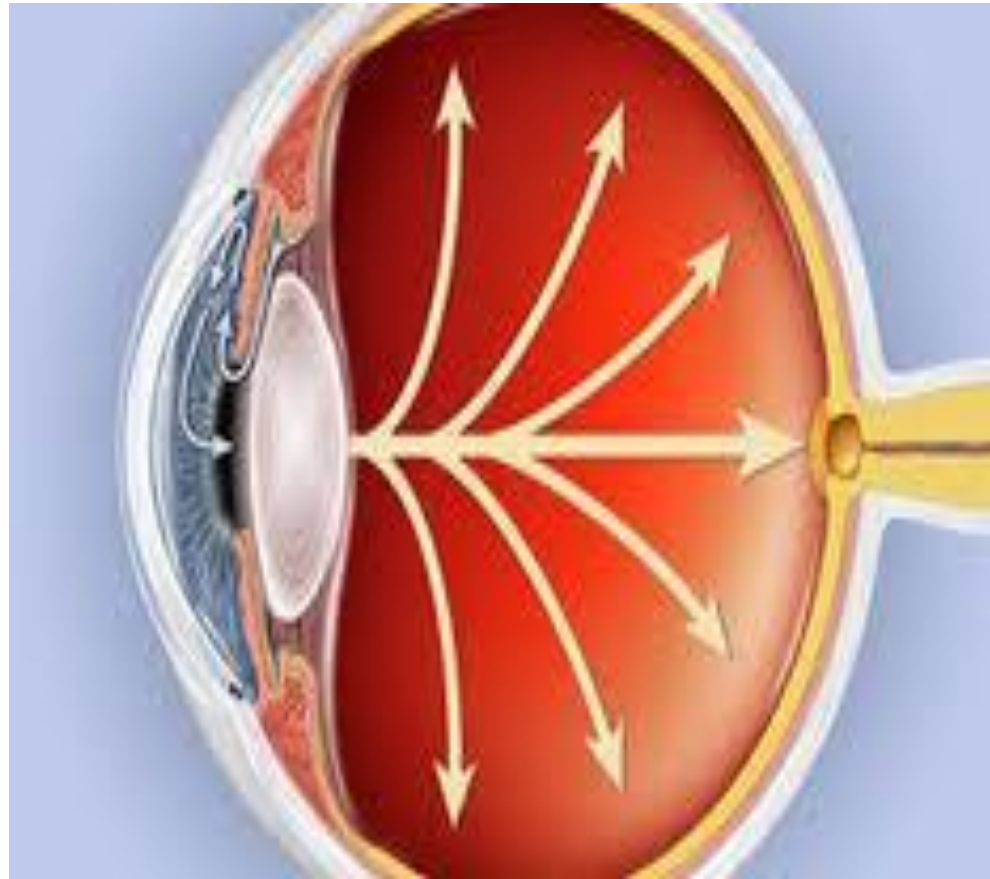
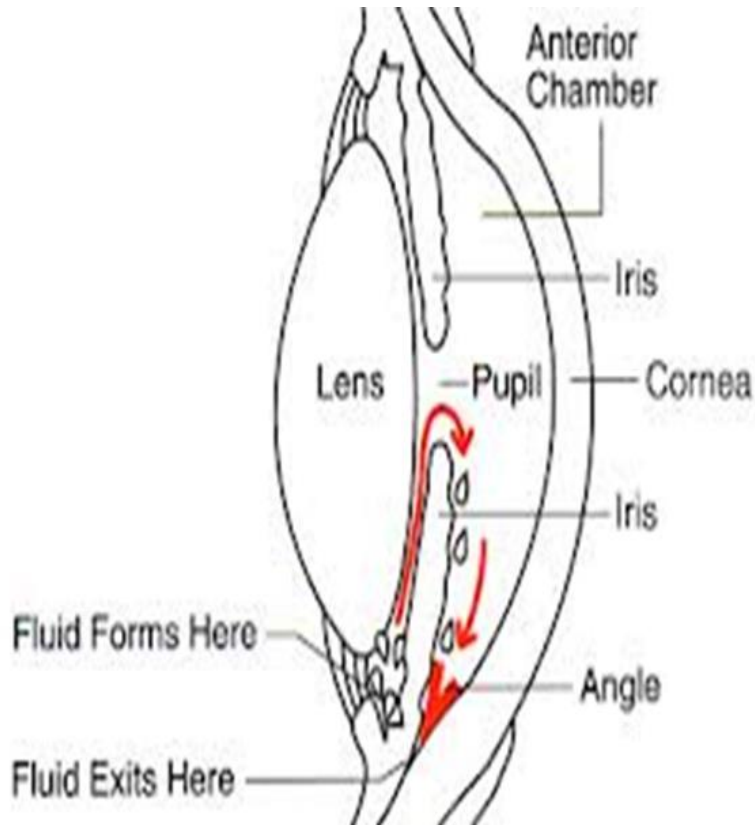
Visit www.aht.org.uk/giftofight to find out more about the AHT's glaucoma project or to make a donation through the Gift of Sight Appeal. Alternatively, you can find the AHT at Crufts, in hall 3, stand 65.



What is glaucoma?

- Disease of the eye characterised by high intraocular pressure
- Occurs as a result of abnormal drainage of fluid from the eye
- High pressures leads to irreversible damage to retina and optic nerve

What is glaucoma?



What causes glaucoma?

- Secondary
 - Inflammation
 - Tumours
 - Bleeding
 - Lens luxation
- Primary
 - Inherited abnormality in fluid drainage pathway of the eye

Inherited (primary) glaucoma

- Two types
 - 1. Primary Open Angle Glaucoma**
 - Less common
 - Few breeds
 - Drainage angle of eye appears normal
 - 2. Primary Closed Angle Glaucoma**
 - Common
 - Many breeds
 - Drainage angle of eye appears abnormal
 - ‘Goniodysgenesis’ or ‘PLD’

Inherited (primary) glaucoma

- Both types of primary glaucoma
 - Painful
 - Blinding
 - Expensive and difficult to treat
 - Most dogs require eye removal

Primary Open Angle Glaucoma

- The fluid drainage abnormality cannot be screened for by examination
- Seen in
 - Petit Basset Griffon Vendéen
 - Beagle
 - Basset Fauve de Bretagne
 - Sharpei
 - Basset Hound
- Simple inheritance, autosomal recessive

Primary Open Angle Glaucoma

- Gradually progressive
- Initially responds to eye drops
- Eventually blinding
- Eyes need to be removed
- Petit Basset Griffon Vendéen
- Mutation responsible discovered at AHT
- DNA test launched at Crufts 2015



Primary Open Angle Glaucoma

- **Basset Hound**

- POAG not reported in this breed

- November 2014

- 230 BH eye tested at routine screening sessions

- 3 cases POAG discovered

- January 2015

- Mutation discovered

- 16% carriers

- April 2015

- DNA test launched



The screenshot shows the Animal Health Trust (AHT) website. At the top, there is a navigation bar with links for 'About us', 'AHT Jobs', 'Press', 'Vets', and 'Scientists'. Below this is the AHT logo and the tagline 'The charity fighting disease and injury in animals'. A secondary navigation bar includes 'Home', 'What we do', 'What you can do', 'News', and 'Donate'. The main content area features a news article published on 09/06/2015 at 10:07:16. The article title is 'AHT DISCOVERS NEW FORM OF GLAUCOMA IN BASSET HOUNDS AND LAUNCHES DNA TEST'. To the right of the text is a photograph of a man sitting on the grass with several Basset Hound dogs.

Importance of routine eye testing

- Annual eye test (not gonioscopy) advised
 - It's a whole eye test!
 - Not just for PRA or cataract!!!
- New inherited eye diseases emerge all the time
- Painful and sight-threatening
- Early recognition leads to early eradication
- Minimises pain, blindness and cost!!!

Primary Open Angle Glaucoma

- **Basset Fauve de Bretagne**
 - October 2014
 - 3 cases of POAG
 - Screened 24 normals
 - January 2015
 - Mutation discovered
 - DNA test possible

Primary Closed Angle Glaucoma

- 40 breeds reported to be affected worldwide
- In UK ~ 15 breeds commonly present for primary glaucoma
- >1500 dogs in UK affected each year
- Associated with PLD in several breeds



Primary Closed Angle Glaucoma

- Sudden onset
- Very painful
- Responds very poorly to medication
- Most (nearly all) dogs require eye removal on welfare grounds
- The risk factor CAN be screened for by examination
- Affected dogs removed from breeding pool

Signs of Glaucoma

- Cloudiness of front of eye
- Redness around eye
- Loss of vision
- Pain



Diagnosis of Glaucoma

Eye pressure measurement



Treatment of Glaucoma

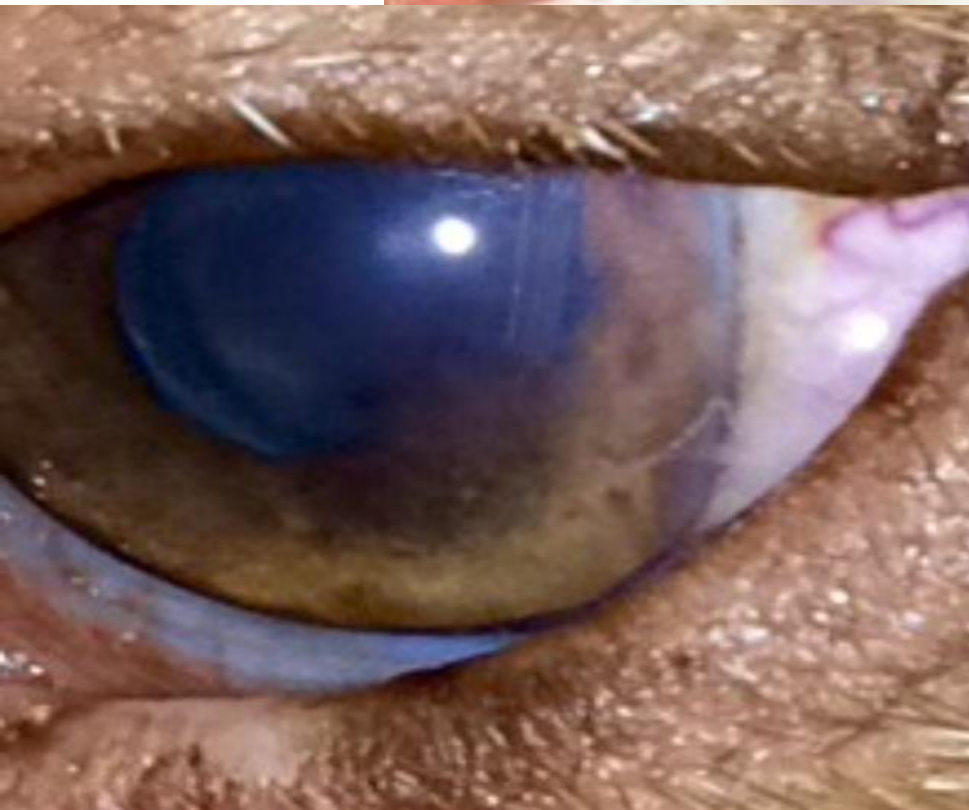
- **Medical**

- Eye drops
- To reduce fluid production inside the eye
- To increase fluid drainage from the eye

- **Surgical**

- To reduce fluid production
 - Destruction of part of the eye
- To increase fluid drainage
 - Insert a valve implant

ECP Treatment of Ciliary Body



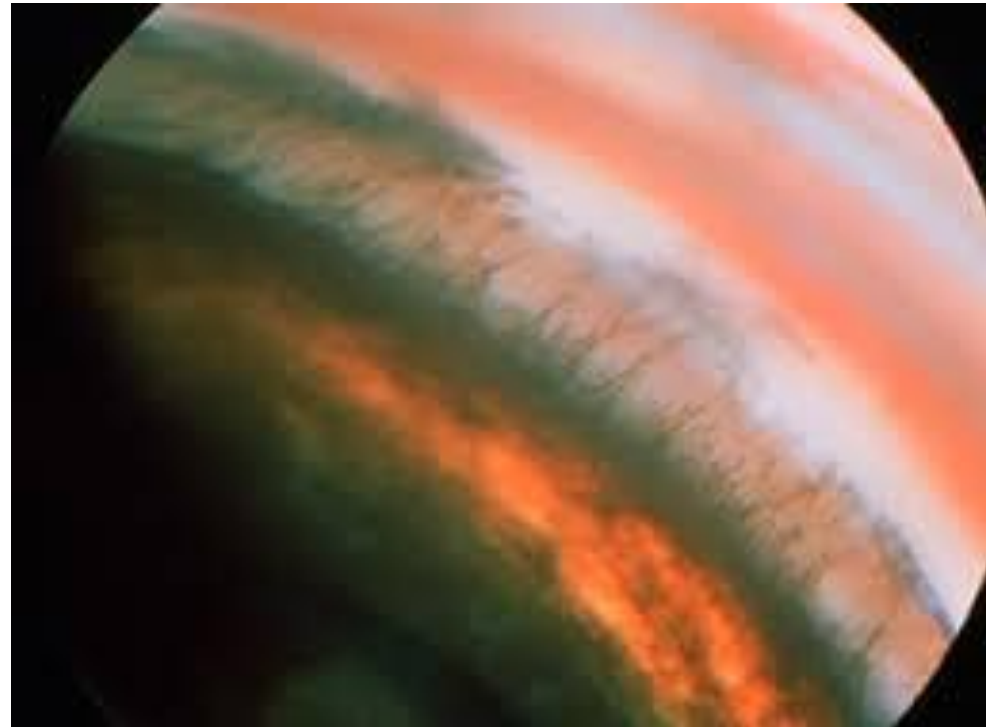
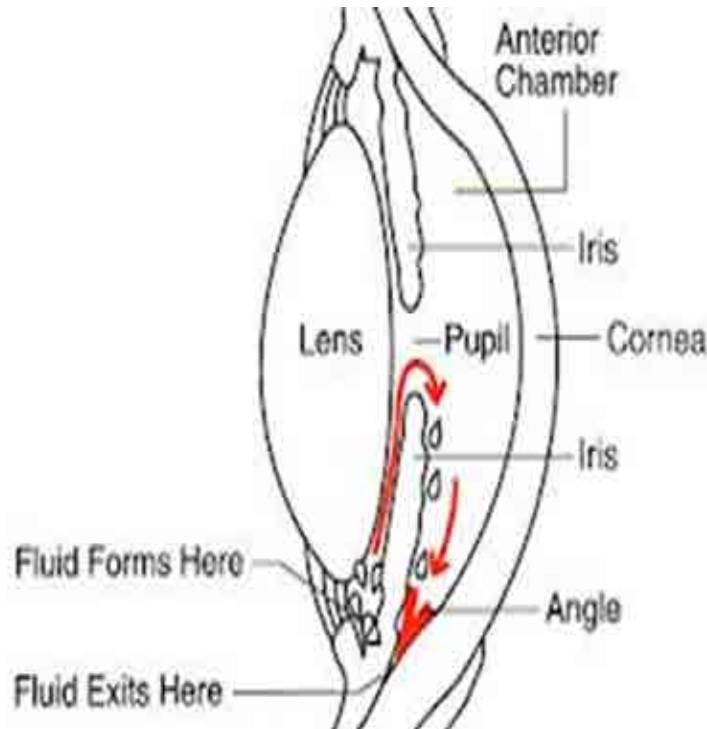
PLD

- Abnormality of the drainage (iridocorneal angle) of the eye
- Also known as pectinate ligament dysplasia
- Assessed by gonioscopy

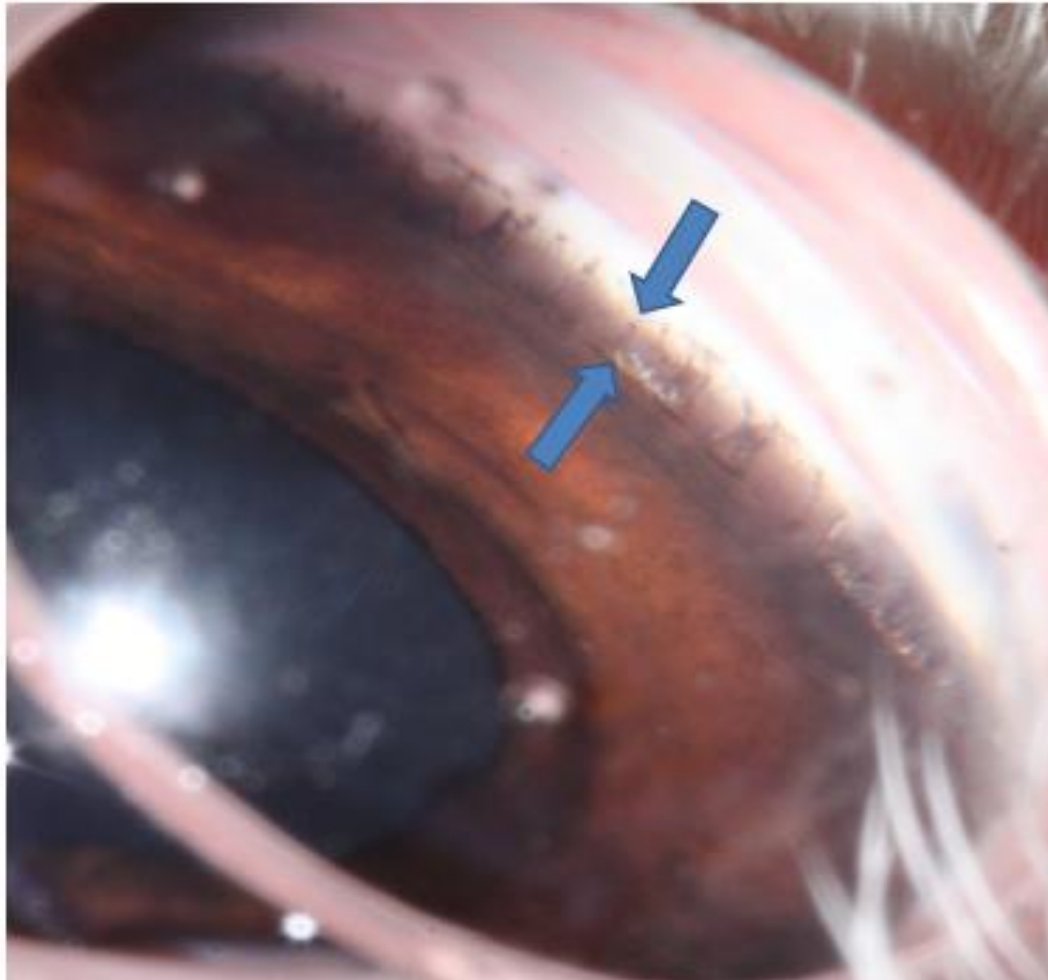


Gonioscopy

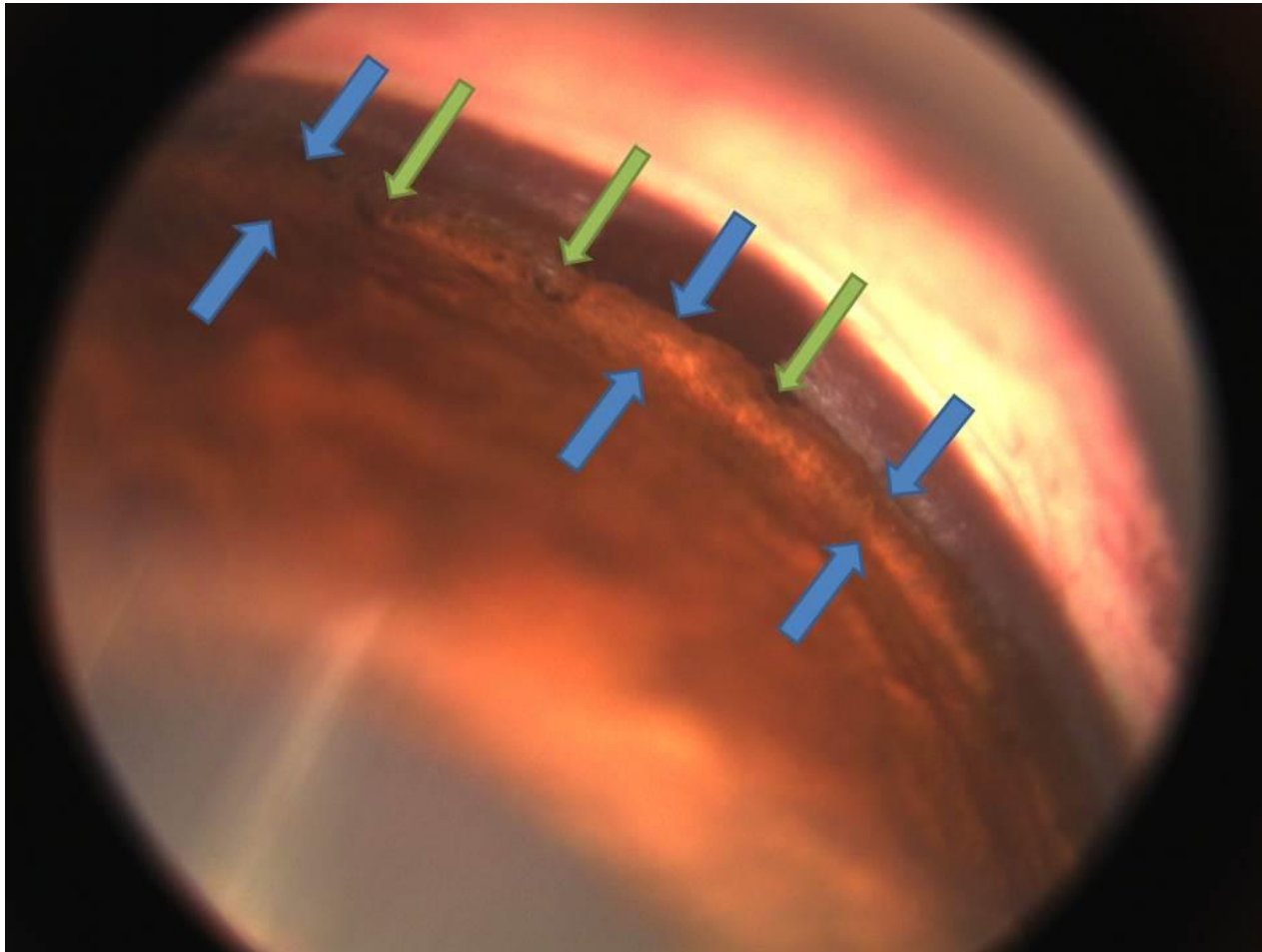
- PLD = prerequisite for glaucoma
- Not all dogs with PLD will develop glaucoma



No PLD



Severe PLD, few 'flow holes'



Primary Closed Angle Glaucoma

- PLD shown to have relatively high heritability
 - Flatcoated Retriever (0.7)
 - Wood et al (1998)
 - Animal Health Trust
- Inheritance unknown
- Not simple recessive (unlike POAG)
- More than one gene/mutation likely to be involved

Gonioscopy under the BVA Scheme

- 'One off test' performed before breeding
- Judge to be 'affected' if 20-25% or more of the drainage angle is abnormal
- Breeding advised against
- Breed to 'unaffected'???
- Yes (in theory) for POAG

Gonioscopy under the BVA Scheme

- In Flatcoated Retrievers it can progress over time
- Pearl et al. (Veterinary Ophthalmology 2015)
- Progresses in 40% dogs
- In FCR now recommended every 3 years

PLD and Glaucoma: Our Project

- **What we think:**
 - Genetics of PLD simpler than glaucoma
 - PLD and glaucoma cases will share genetic variations not found in unaffected (control) cases
 - Glaucoma cases may have additional genetic variations

Schedule A Breeds

Basset Hound

Welsh Springer Spaniel

Flat Coated Retriever

Siberian Husky

American Cocker Spaniel

Cocker Spaniel

English Springer Spaniel

Spanish Water Dog

Schedule B Breeds

Dandie Dinmont Terrier

Border Collie

Hungarian Vizsla

Leonberger

Golden Retriever

Our Project

- Perform gonioscopy
- Take eye pressure readings
- Collect samples (cheek swabs)
- Calculate prevalence of PLD in each breed
- In WSS only, investigate if PLD is progressive
- Compare the DNA in search of variations

Genetic analysis

- For each breed
 1. Dogs with normal eyes (≥ 5 years old)
 2. Dogs with PLD
 3. Dogs with primary glaucoma
- Compare DNA between the 3 groups
- Find differences in genetic code
- Develop DNA tests

Sample Collection

- Breed shows
- Breeder home visits
- AHT Open Days
- Reviewing BVA & ECVO certificates
- Clinical cases at AHT and around the world

–**More than 1500 samples**

Results so far: PLD Prevalence between breeds

- Basset Hound = 38.4%
- Welsh Springer Spaniel = 36.2%
- Flatcoated Retriever = 21.2%
- Dandie Dinmont Terrier = 22.1%
- Golden Retriever = 31.8%

Results so far: PLD progression

- In all breeds studied thus far PLD rate increases with age
- Suggests that PLD is progressive
- We have shown PLD to progress with time in individual WSS to the extent that some develop glaucoma

Results so far: genetics

- We have screened the entire DNA of 300 dogs (FCRs and WSSs)
 - £130 per dog
 - £40,000 total
- We are 'fine toothcomb-screening' the DNA of 5 dogs
 - £2000 per dog
 - £10,000
 - We have blood from 1 HV with glaucoma!

Results so far

- Found mutation responsible for POAG in two dog breeds
- Reported prevalence of PLD in WSS (and 3 other breeds)
- Shown conclusively that PLD is progressive in WSS
- Are narrowing down on the mutation responsible for glaucoma in the WSS and FCR

On going plans

- We have a lot more DNA to analyse
- What we learn from one breed will probably help other breeds
- Investigate relationship between POAG and PCAG
- We will continue to collect more samples
- We will continue to secure more funding
- **We will continue to make progress!**