The Genetics of Canine Glaucoma

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The Supervisors

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• 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 £300,000 from Dogs Trust, hopes to identify the mutations responsible for goniodysgenesis and eradicate them from the gene pools of affected breeds.

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 (ACG) 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/IDSA eye scheme before breeding.

For now the best way to prevent primary glaucoma is to contribute to the research. Dr Cathryn Mellor (pictured below right), head geneticist at the Kennel Club Genetice 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 Vendeen.

“With the help of the AHT, we have been able to develop a new test that can identify the affected gene in the Petit Basset Griffon Vendeen. This would not have been possible without the input from the people who own and breed these dogs.” said she. “It is still a long way to go, but we are making progress, and we hope to be able to offer this test in the near future.”

Visit www.aht.org.uk/glaucoma to find out more about the AHT’s glaucoma project and 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
   - ‘Goniodygenesis’ 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 Vendeen
  - 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 Vendeen
- 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
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
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
Severe PLD, few ‘flow holes’
Primary Closed Angle Glaucoma

• PLD shown to have relatively high heritability
  – Flatcoated Retriever (0.7)
  – 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
<table>
<thead>
<tr>
<th>Schedule A Breeds</th>
<th>Schedule B Breeds</th>
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<tr>
<td>Basset Hound</td>
<td>Dandie Dinmont Terrier</td>
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<tr>
<td>Welsh Springer Spaniel</td>
<td>Border Collie</td>
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<tr>
<td>Flat Coated Retriever</td>
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<td>Cocker Spaniel</td>
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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!**