ACVO Genetics Mtg: 11/4/09

The blue book/CD – a source of wisdom or a mistaken (confusing?) guide?

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University of Pennsylvania

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co-owner, consultant and holder of patents for mutations and DNA tests
Inherited Eye Diseases-Relevant Facts

# 1 Ophthalmologists (in)correctly believe that they have subspecialty training in genetics.
# 2 The "Bible" of ophthalmology is full of unknowns, …
A nutritional deficiency of vitamin E and other antioxidants, not an inherited disease

conformation

...and many 'facts' are often incorrect.

survey; NO data

1399 dogs (5.5% PPS); pedigrees insufficient to support/refute AD inheritance; AR most likely

Wrong reference

1. AGVO Genetics Committee, 1993 and/or: Data from CERF All Breeds Report, 1991-1993.
# 3 Inherited eye diseases are more frequent in dogs than cats

- Although there is a formal registration program for canine eye diseases in US (ACVO through CERF), continental Europe (through ECVO) and UK (BVA/KC "scheme"), veterinary ophthalmologists do examine cats, yet inherited eye diseases are rarely identified or reported in cat breeds.

<table>
<thead>
<tr>
<th></th>
<th>Dog</th>
<th>Cat</th>
</tr>
</thead>
<tbody>
<tr>
<td>cataract</td>
<td>&gt;30-40*</td>
<td>2</td>
</tr>
<tr>
<td>PRA</td>
<td>&gt;15**</td>
<td>3***</td>
</tr>
</tbody>
</table>

(retinal diseases)

* major inherited eye problem; many breeds
** >50-70 breeds affected with PRA/retinal diseases
*** 2 in general population; one in research lab
Just because a trait is inherited, it is not inherently BAD

ERG amplitudes and waveforms are breed-specific

German shepherd

Golden retriever

Labrador-Golden cross and backcross

Labrador retriever

Light Adapted

Dark Adapted (20 min)

n=420

n=98

n=60

n=1089
INDICATION THAT A DISEASE IN A BREED HAS A GENETIC CAUSE

1. Greater frequency of the specific disorder within a group of related individuals (within family group, strain or breed) than in general population.

2. Increase in frequency of disorder with inbreeding (for single recessive or polygenic disorders).

3. Characteristic age of onset, clinical signs and course of disease.

4. Presence of disease in another breed where it has been shown to be inherited.

Dr. Don Patterson
Genetic Heterogeneity

*Genetic Heterogeneity* (two or more fundamentally distinct entities that share approximately the same phenotype) is the rule. If a disorder is thought to be a single entity, it usually means that the disorder is not well understood.

*Victor McKusick, 1972*
How to Study and Characterize a Genetic Disorder

- Get historical information on disease.
- First source pedigree information. Don't rely on hearsay.
- **DO THE EXAMINATIONS YOURSELF !!!!!!**
- Use the appropriate equipment for disease studied.
- Be a "splitter" NOT a "lumper" when characterizing the phenotype.
- Trust yourself and NO ONE ELSE.
- Some breeders are very helpful, others (most?) are not.
- Some diplomates (ACVO, ECVO) are helpful, many are not because diagnoses are wrong or inconsistent.
- **More important to be consistent in your diagnoses, rather than "correct". You can always change an incorrect diagnosis that is consistently made.**
- Be aware of the literature, and interpret your findings conservatively.
- If you make a finding, publish the results. **If not published, it enters the vast repository of useless, anecdotal, genetic ophthalmology.**
Monogenic Disorders

- Predictable age of onset, and disease progression
- Predictable phenotype
- Predictable disease course
- Predictable outcome
- Predictable inheritance pattern

Polygenic Disorder

- Variable age of onset, and progression
- Variable phenotype
- Variable disease course
- Variable outcome
- Unpredictable inheritance

PREDICTABILITY !!!!!!!!!!!!

Variability is predictable !!!
Examples of Single Gene Defects and Polygenic Disorders

Single Gene Defect          Polygenic Disorder
Siberian Husky: Crystalline Corneal Dystrophy

Fig 4—Drawing of crystalline corneal opacities in Siberian Huskies demonstrates the typical gray ring and the clear central and peripheral cornea. The crystals occupy the pre-Descemet’s stroma. Slit views A through E represent five commonly seen patterns: (A) refractile polychromatonic crystals in the posterior stroma adjacent to Descemet’s membrane; (B) gray-brown, homogeneous, smudgy deposits within the anterior stroma and the crystals in the posterior stroma, with clear stroma in between; (C) gray-brown, homogeneous deposits in the anterior stroma, with the remainder of the stroma clear; (D) gray-brown, homogeneous deposits involving the posterior two-thirds of the stroma; and (E) gray-brown, homogeneous deposits involving the entire stromal thickness.
Outcross to Samoyeds established that it is neither dominant or X-linked. Affected x Affected crosses established AR inheritance.
Cholesterolosis
(lipid dystrophy?)

There is NO basis for cholesterolosis (corneal lipid deposits) being inherited. Should it still be grouped under the corneal dystrophy category that implies an inherited disorder?
Shetland Sheepdog: Familial Epithelial-Stromal Dystrophy

Min. Wirehaired Dachshund: Superficial Punctate Keratopathy

### Examples of Single Gene Defects and Polygenic Disorders

<table>
<thead>
<tr>
<th>Single Gene</th>
<th>Polygenic</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Crystalline corneal dystrophy (Sib. Husky)</td>
<td>• Ep/Strom Dyst (SS)</td>
<td>• Punct Keratop (Dachs)</td>
</tr>
</tbody>
</table>

### Not Inherited:
- • Cholesterolosis
Selected Inherited Cataracts

<table>
<thead>
<tr>
<th>I. HORSE</th>
<th>II. CAT</th>
<th>III. DOG</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BREED</strong></td>
<td><strong>INHERITANCE</strong></td>
<td><strong>AGE OF DIAGNOSIS</strong></td>
</tr>
<tr>
<td>Morgan</td>
<td>dominant</td>
<td>congenital</td>
</tr>
<tr>
<td>British shorthair</td>
<td>recessive</td>
<td>congenital</td>
</tr>
<tr>
<td>Himalayan</td>
<td>recessive</td>
<td>12 wks</td>
</tr>
<tr>
<td>Miniature schnauzer</td>
<td>recessive</td>
<td>congenital</td>
</tr>
<tr>
<td>Old Eng sheepdog</td>
<td>--</td>
<td>congenital/adult</td>
</tr>
<tr>
<td>Cav King Charles span</td>
<td>--</td>
<td>congenital</td>
</tr>
<tr>
<td>German shepherd</td>
<td>dominant</td>
<td>congenital</td>
</tr>
<tr>
<td>German shepherd</td>
<td>recessive</td>
<td>&gt;8-12 wks</td>
</tr>
<tr>
<td>West Highland white</td>
<td>--</td>
<td>6 ms-1 yr</td>
</tr>
<tr>
<td>Siberian husky</td>
<td>--</td>
<td>8 ms-1.5 yrs</td>
</tr>
<tr>
<td>Golden retriever</td>
<td>incomplete dominant</td>
<td>8 ms-2 yrs</td>
</tr>
<tr>
<td>Standard poodle</td>
<td>--</td>
<td>&gt;1-2 yrs</td>
</tr>
<tr>
<td>Cheasapeake Bay ret</td>
<td>--</td>
<td>&gt;1-1.5 yrs</td>
</tr>
<tr>
<td>Labrador retriever</td>
<td>incomplete dominant</td>
<td>&gt;1-2 yrs</td>
</tr>
<tr>
<td>Eng springer spaniel</td>
<td>--</td>
<td>1-2.5 yrs</td>
</tr>
<tr>
<td>Afghan hound</td>
<td>--</td>
<td>1-2 yrs</td>
</tr>
<tr>
<td>Boston terrier</td>
<td>recessive</td>
<td>1-3 yrs/&gt;6 yrs</td>
</tr>
<tr>
<td>Labrador retriever</td>
<td>--</td>
<td>4-7 yrs</td>
</tr>
<tr>
<td>Toy/Min poodle</td>
<td>--</td>
<td>3-7 yrs</td>
</tr>
<tr>
<td>Am cocker spaniel</td>
<td>recessive</td>
<td>&gt;1 yr</td>
</tr>
</tbody>
</table>

many more dog breeds are known to have inherited cataracts
Cataract in Labrador and Golden Retrievers

In ~ 95% of dogs, age of onset is 1.2-2 yrs, and cataracts are bilateral. In ~ 5%, they can be unilateral, or develop after 4-6 years of age. Are the latter cataracts inherited ?????
Labrador Retriever-
Alpo food taster

Golden Retriever-
"Seeing Eye" guide
Labrador retriever: inherited cataract

Beagle: drug-induced cataract

"environment"
Suggestion based on NO studies

Cataract

The most frequently reported cataracts in the breed are bilateral or unilateral, focal, posterior polar (posterior cortical)/subcapsular cataracts usually present between 1-3 years of age. These are generally stationary or very slowly progressive and generally do not interfere with vision. It has been suggested that these cataracts are inherited as dominant with incomplete penetrance, but definitive breeding studies are still required to verify this hypothesis.

1399 dogs (5.5% PPS); pedigrees insufficient to support/refute AD inheritance; AR most likely

References


Incorrect data
Approaches to finding a genetic defect:
define the mode of inheritance

Rubin proposed (1973) that inheritance of cataracts in Golden retrievers was dominant with incomplete penetrance. Dogs with the triangular cataracts were heterozygous, and those with the complete cataract were homozygous for the defect.
1.32 yrs
O.D. A P O.S.

1.34 yrs
O.D. A P O.S.

1.6 yrs

2.7 yrs

Fancy: Lab/Golden backcross
Francine: Golden retriever

Honor: German shepherd
Fancy: Lab/Golden retriever backcross
Francine: Golden retriever
# Observed and Expected Outcomes Based on Autosomal Dominant Inheritance

<table>
<thead>
<tr>
<th>Penetrance</th>
<th>Unilateral cataract</th>
<th>Bilateral cataract</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed*</td>
<td>Expected</td>
</tr>
<tr>
<td>Complete</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>75%</td>
<td>0</td>
<td>5.3</td>
</tr>
<tr>
<td>50%</td>
<td>0</td>
<td>3.5</td>
</tr>
<tr>
<td>25%</td>
<td>0</td>
<td>1.8</td>
</tr>
</tbody>
</table>

*14 progeny* produced (12 survived) from unilateral cataract outcross; all >3 years of age.

**21 progeny** produced from bilateral cataract outcross; all >3 years of age.
Characterization and prevalence of cataracts in Labrador Retrievers in The Netherlands

Ingrid M. G. Kraijer-Huver, DVM; Ed J. Gubbels, Jr.; Janneke Scholten; Sylvia C. Djadjiningrat-Laanen, DVM; Michael H. Boevê, DVM, PhD; Frans C. Stades, DVM, PhD

<table>
<thead>
<tr>
<th>Type of cataract*</th>
<th>Non-PRA-affected dogs (%)</th>
<th>PRA-affected dogs (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>244 (76.8)</td>
<td>39 (34.5)</td>
</tr>
<tr>
<td>II</td>
<td>23 (7.2)</td>
<td>25 (22.1)</td>
</tr>
<tr>
<td>III</td>
<td>51 (16.0)</td>
<td>49 (43.4)</td>
</tr>
<tr>
<td>Total</td>
<td><strong>318</strong></td>
<td><strong>113</strong></td>
</tr>
</tbody>
</table>

Data are presented as number of dogs (%).

*Hereditary (mostly cortical) cataracts were classified as 1 of 3 types as follows: type I = PPC; type II = extensive immature and mature cataract; and type III = miscellaneous, including anterior suture line, punctata, cortical, and nuclear cataracts.
# Examples of Single Gene Defects and Polygenic Disorders

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**Not Inherited:**

• Cholesterololis
Persistent Pupillary Membranes (PPMs)

- Congenital acquired or inherited defect of the anterior segment (tunica vasculosa lentis =TVL)
- Inherited defect in several breeds:
  - Basenji, Pemb. or Card. Welsh Corgi, Chow Chow, Collie, Englshih mastiff, others
- **Polygenic** inheritance

Fig. 102. Persistent pupillary membrane
Frontal and cross-section view showing all variations of persistent pupillary membrane.

- a) One end floating free in anterior chamber
- b) Iris to lens — causes capsular cataract.
- c) Iris to iris — no clinical significance.
- d) Iris to cornea — causes adherent leukoma.

Schematic figure from Glenn Severin's notes.
Polygenic Disorder

- Variable age of onset, and progression
- Variable phenotype
- Variable disease course
- Variable outcome based on parental phenotypes
- Unpredictable inheritance

Variability is predictable !!!

Aim for controlling polygenic diseases
Control of Polygenic Diseases: Conventional Approaches

- **Know genetics; recognize phenotype/genotype**

  intensity $\times$ accuracy $\times$ genetic variation

  Selection response = 

  generation interval

- **Intensity**: fraction kept as parents; few $\rightarrow$ greater response
- **Accuracy**: how well the genetic merit of animals is estimated
- **Genetic variation**: greater variation $\rightarrow$ greater response
- **Generation interval**: average age of parents; the longer the interval, the slower the change

Aguirre :10/09
Modified from John Pollak
**Examples of Single Gene Defects and Polygenic Disorders**

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**Not Inherited:**

• Cholesterolosis
Retinal Dysplasia

• Generalized
  – Inherited

• Focal / Multifocal or Geographic
  – Sporadic
  – Inherited

• Oculo-skeletal Dysplasia
  – Inherited
Retinal Dysplasia: Focal / Multifocal

Inherited Form

Autosomal recessive in English springer spaniel.

Disease is usually non-progressive, but in some dogs focal detachments can develop that progress to complete detachment.
Retinal Dysplasia: Focal Multifocal (Folds) Sporadic Form

Familial inheritance proposed for Am. Cocker spaniel. No other studies carried out.

Characteristic lesions = retinal folds; single or multiple
Retinal Dysplasia: Geographic-Sporadic Form

Other than the increased frequency in some breeds, e.g. Cav KC Span, there is no evidence for heritability.
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<tr>
<td>• Ret. Dysp. (ESS)</td>
<td></td>
<td>• Folds (all /most breeds)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Geog. Ret Dysp</td>
</tr>
</tbody>
</table>

**Not Inherited:**

• Cholesterolosis
Oculo-Skeletal Dysplasia (osd1, osd2): heterozygotes have focal / multifocal retinal dysplasia

**homozygous affected**
- short-limbed dwarfism
- cataracts
- retinal detachment
- other ocular defects

**heterozygous**
- normal skeleton
- retinal folds +/-

**now that a mutation test is available do DNA test:**
Normal test=folds insignificant
Mutation=follow OG recommendations
The mutation causes choroidal hypoplasia. A second AR modifier locus is likely responsible for the colobomas, and needs the mutation in the primary gene to be expressed.
CEA: Choroidal Hypoplasia
<table>
<thead>
<tr>
<th>Year (dogs reported)</th>
<th>Choroidal Hypoplasia</th>
<th>Coloboma</th>
<th>Retinal Detachment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991 (2599)</td>
<td>69%</td>
<td>8%</td>
<td>3%</td>
</tr>
<tr>
<td>1998 (2845)</td>
<td>67%</td>
<td>8%</td>
<td>1%</td>
</tr>
<tr>
<td>2008 (1797)</td>
<td>72%</td>
<td>1%</td>
<td>2%</td>
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*Limited to smooth and rough collies-unilateral and bilateral lesions grouped*
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<td>• CEA (Colob /Ret det ?)</td>
<td></td>
</tr>
<tr>
<td>• CEA (Ch Hypoplasia)</td>
<td></td>
<td></td>
</tr>
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Not Inherited:
• Cholesterolosis
Confusing statements for breeders and diplomates

MASTIFF

K. Retinal atrophy - generalized
   Dominant  1,4,5,6  NO

K. Retinal atrophy-generalized

A degenerative disease of the retinal visual cells which progresses to blindness. This abnormality, also known as progressive retinal atrophy or PRA, may be detected by electroretinogram (not part of a routine eye screening examination) before it is apparent clinically. Except for X-linked PRA in the Siberian Husky, in all breeds studied to date, PRA is inherited as an autosomal recessive trait.

For DNA testing contact Optigen®: Dominant PRA test. Optigen LLC, Cornell Business and Technology Park, 33 Thornwood Dr., Suite 102, Ithaca, NY 14850. Telephone: 607-257-0301. E-mail: genetest@optigen.com ; website: www.optigen.com.

BULLMASTIFF

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>INHERITANCE</th>
<th>REFERENCE</th>
<th>BREEDING ADVICE</th>
</tr>
</thead>
<tbody>
<tr>
<td>H. Retinal atrophy</td>
<td>Autosomal</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>recessive</td>
<td></td>
<td></td>
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* A mutation-based DNA test is available for dominant PRA.

H Retinal atrophy-generalized

A degenerative disease of the retinal visual cells which progresses to blindness. This abnormality, also known as progressive retinal atrophy or PRA, may be detected by electroretinogram (not part of a routine eye screening examination) before it is apparent clinically. Except for X-linked PRA in the Siberian Husky, in all breeds studied to date, PRA is inherited as an autosomal recessive trait.

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Suggestions for Improvements

• Merge ACVO and ECVO Genetics Committees.
• Simplify the Blue Book
  - be more critical in review of publications.
  - just because it is published does not mean it is correct.
  - for each breed, only include in the "Disorders" those that are shown to be inherited based on actual publications.
  - at the end, include those are are suspected to be inherited, but do not use the "ACVO Genetics Committee and/or Data from CERF all breed reports" as the default reference. Use this only as an "early warning system" to make breeders and diplomates aware of problems that are potentially inherited.
  - anecdotal ophthalmology references should be eliminated.
  - abstract references should have a natural lifespan of 2 years or less. If not published within 2 years, results are likely incorrect or not worth publishing.
• End result will be a smaller Blue Book with more accurate information.
Educational / Training Opportunities

Veterinary Medical Genetics Training Grant (NIH) has/will have open slots in the training program to investigate cellular and molecular mechanisms of eye (retina/glaucoma/other) disease, or to develop therapies for these diseases:

• Post doctoral fellowships
• PhD training

Requirements:
- US citizenship or green card; veterinary degree
- Board certification or eligibility (ACVO / ECVO) desirable but not required
- educational loan payback programs may be possible through NIH.

Contact:
Gustavo Aguirre
gda@vet.upenn.edu

Faculty members:
G. Aguirre
W. Beltran
A. Komaromy