INHERITED CARDIOMYOPATHIES-
UNDERSTANDING CLINICAL & GENETIC
ASPECTS FOR YOUR BREED

Kathryn M. Meurs, DVM, PhD
Diplomate ACVIM (Cardiology)
North Carolina State University
Understanding inherited heart disease

Inherited (familial) heart disease
- Genetically programmed to develop the disease
- Can be both congenital or adult onset

Some diseases may be familial but not develop until the dog is an adult (dilated cardiomyopathy for example)
Understanding familial heart disease

Although a disease of the same name may appear in several breeds, it may not be identical in the different breeds.

- Use caution when interpreting clinical or genetic data from one breed to another.
Understanding familial heart disease

Three step approach

- Characterizing your disease (PHENOTYPE)
- Characterizing the familial aspects (mode of inheritance) of your disease
- Characterizing the molecular aspects of your familial heart disease (can you get a test?!)
Dilated Cardiomyopathy

- Heart muscle disease

- Adult onset (majority of cases), usually > 5 years

- Common affected breeds include Doberman pinscher, Great Danes, Irish Wolfhounds, Scottish Deerhounds, Newfoundlands
Dilated Cardiomyopathy
Understanding familial heart disease

Characterizing your disease (PHENOTYPE)
Understanding familial heart disease

Characterizing the familial aspects (mode of inheritance) of your disease
Inheritance

Dilated cardiomyopathy is inherited as an AUTOSOMAL DOMINANT trait in the Doberman pinscher

• Not carried on a sex chromosome

• If the dog has one copy of the gene they may show the disease
Doberman pinschers with DCM
Understanding familial heart disease

Characterizing the molecular aspects of your familial heart disease
Dilated Cardiomyopathy in the Doberman Pinscher

• In human beings > 20 different genes have been shown to cause DCM

  A mutation in each one of those genes, separately, can cause the disease
Dilated Cardiomyopathy in the Doberman Pinscher

Normal

Homozygous Deletion
Cardiac Mitochondria

Mitochondria are demonstrated to be abnormal by electron microscopy which may be a consequence of abnormal energy

Doberman DCM

Normal
Factors unknown - Are there other causes?

• In humans beings, causative mutations for DCM have been identified in 24 different genes!

• Some evidence that DCM in European Doberman pinschers may be different

• Therefore, it is unfortunately likely that this will be the > 1 in the Doberman pinscher!
Genetic Penetrance

• In human beings, DCM is a disease with age related, relatively low penetrance

• Penetrance = how much the disease penetrates that individual

• In some human families only 20-30% of people with the mutation will show the disease
  • 80% with mutation will never develop clinically significant disease
Genetic Penetrance

- Mechanism of variable penetrance is poorly understood
- Likely involves environmental or genetic factors
  - Diet?
  - Genetic background?
  - Daily activities?
How do you use this information to guide your program

- At this time we can identify who has the mutation

- However, we can not predict the penetrance

- This means we know who has the mutation, but not who will definitely show the disease
  - May gain some of this from looking at family history
Great Dane Dilated Cardiomyopathy
Understanding familial heart disease

Characterizing your disease (PHENOTYPE)
Dilated Cardiomyopathy

• Although dilated cardiomyopathy on an echocardiogram or at death looks the same regardless of breed, it is not really all the same disease

• Dilated cardiomyopathy in the Great Dane IS NOT the same as the Doberman pinscher
Great Dane Dilated Cardiomyopathy

North America:

- Males more than Females
- 7 years of age or older
- Large dilated heart
- Rapid heart rate (atrial fibrillation)
NORMAL DOG

Great Dane DCM
Great Dane Dilated Cardiomyopathy

North America:
- Males more than Females
- 7 years of age or older
- Large dilated heart
- Rapid heart rate (atrial fibrillation)

European (but also seen here)
- Both sexes
- Young dogs (less than 2 years)
- Sudden death
Great Danes

Dilated cardiomyopathy in the Great Dane is inherited as an X-LINKED trait in at least some families:

- Trait carried on the X chromosome
- If male dog has the trait he will show the disease
- Females may be silent carriers
Great Dane
Doberman pinschers with DCM
Inheritance

- The different pattern of inheritance tells us that the underlying cause is DIFFERENT.

- There are likely to be numerous different causes of dilated cardiomyopathy in the dog (even within the same breed!!!)

- Genetically complex diseases!!!!
Understanding familial heart disease

Characterizing the molecular aspects of your familial heart disease
Characterizing the molecular aspects of your familial heart disease

Just starting this study this fall!

Samples already collected but more are welcome!

Stay tuned
Boxer Arrhythmogenic right ventricular cardiomyopathy (ARVC)
Understanding familial heart disease

Characterizing your disease (PHENOTYPE)
Boxer Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

- Heart muscle disease (cardiomyopathy)

- Adult onset - 6-8 years of age is average age of onset

Normal dog  ARVC dog
Boxer ARVC
Electrical disease - Identification of ventricular premature complexes

NORMAL DOG

ARVC DOG
Understanding familial heart disease

Characterizing the familial aspects of your disease
Boxer ARVC

• Appears to be inherited as an autosomal dominant trait
• If they have one copy of the gene they can show the trait

• Age related incomplete penetrance
  • Risk of showing clinical signs increase with age
Understanding familial heart disease

Characterizing the molecular aspects of your familial heart disease
A Deletion Mutation is Associated with Disease in Striatin Gene

Normal

Homozygous Deletion
Cardic Desmosome (Hinge)
Dogs homozygous for the mutation appear to have a more severe form of the disease based on abnormal heart beats/24 hours.

Mean = 7860

Mean = 2845

P < 0.05
91% of the time are homozygous for ARVC mutation!
Genetic Penetrance of ARVC in the Boxer

In the Boxer, the disease has about 72% penetrance

• This means that 72% of the dogs with the mutation WILL SHOW the disease

• This means that 28% of the dogs with the mutation WILL NOT SHOW the disease
https://www.facebook.com/BoxerARVC
Breeding Recommendations For Cardiomyopathy with known Mutations
Doberman pinscher DCM and Boxer ARVC

- Genetic testing can be performed
Negative

• Remember that there are many causes for the disease, genetic testing does not mean the dog can not get heart disease

• Just means that the dog will not get the disease from this mutation
Positive Heterozygous

• Increased risk of developing the disease

• Carefully evaluate for signs of disease (Holter monitor, echocardiogram) EVERY YEAR!

• If no evidence of disease and have other positive breed attributes, consider breeding to negative mutation dogs
Positive Heterozygous

Puppies may be screened for mutation and over a few generations, mutation negative puppies may be selected to replace the mutation positive parent
Positive Homozygous

Ideally these are not used for breeding unless:

- Have very positive attributes that need to be maintained in the breed

Only breed to a negative dog
Mutation Screening

It is very likely that there will be a large number of dogs with the mutation in the population.

Removal of all mutation positive dogs is NOT recommended.

Instead, the information should be used to GUIDE your decisions.
Mutation Screening

Use information IN CONJUNCTION with your other health testing (Doppler, DM testing, behavior testing, etc) to make the BEST decisions for your line

NOT INTENDED to be used as a single test to remove or keep a dog in a program
Take Home Points

- Cardiomyopathies are different from breed to breed and each breed will need to do their own evaluations.

- Keys to success are very accurate clinical diagnosis and persistent molecular studies (can take up to 10 years! 😞)

- Once a mutation is identified though, it can be used to make careful educated decisions to reduce disease prevalence.
Thank you

These studies generously funded by:
AKC-CHF
American Boxer Charitable Trust
Pomeranians?