Genetic Veterinary Sciences®, Inc.

Paw Print Genetics

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Genetic Disease Testing the Boykin Spaniel

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BSCBAA Genetics and Health Conversation

Aug 20, 2020

Topic Outline

- Inheritance- Recessive
- Disease Testing-
  - Collie Eye Anomaly
  - Degenerative Myelopathy
  - Exercise-Induced Collapse
  - Progressive Retinal Atrophy, Cone Rod Dystrophy 4
- Inheritance- Dominant
- Disease testing-
  - Intervertebral Disc Disease/Chondrodystrophy (IVDD/CDDY) and Chondrodysplasia (CDPA)

Inheritance Patterns

- Recessive
- Dominant

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Inheritance Patterns: Recessive

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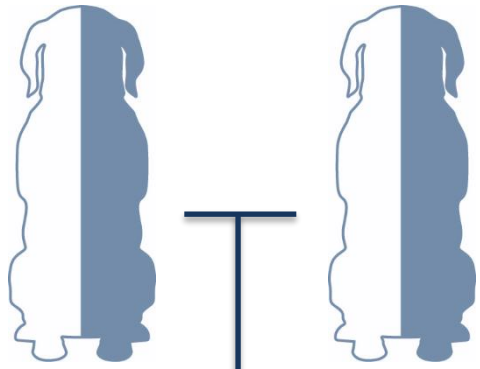
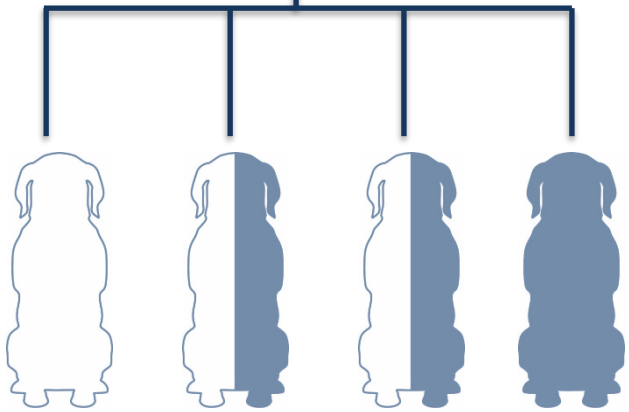
- Recessive diseases- Dog must inherit two copies of the associated genetic mutation (one from each parent) in order to develop the disease
- Dogs with only a single copy of the mutation are considered asymptomatic carriers
- Carriers or affected dogs can produce affected puppies if bred with another dog with the same genetic mutation

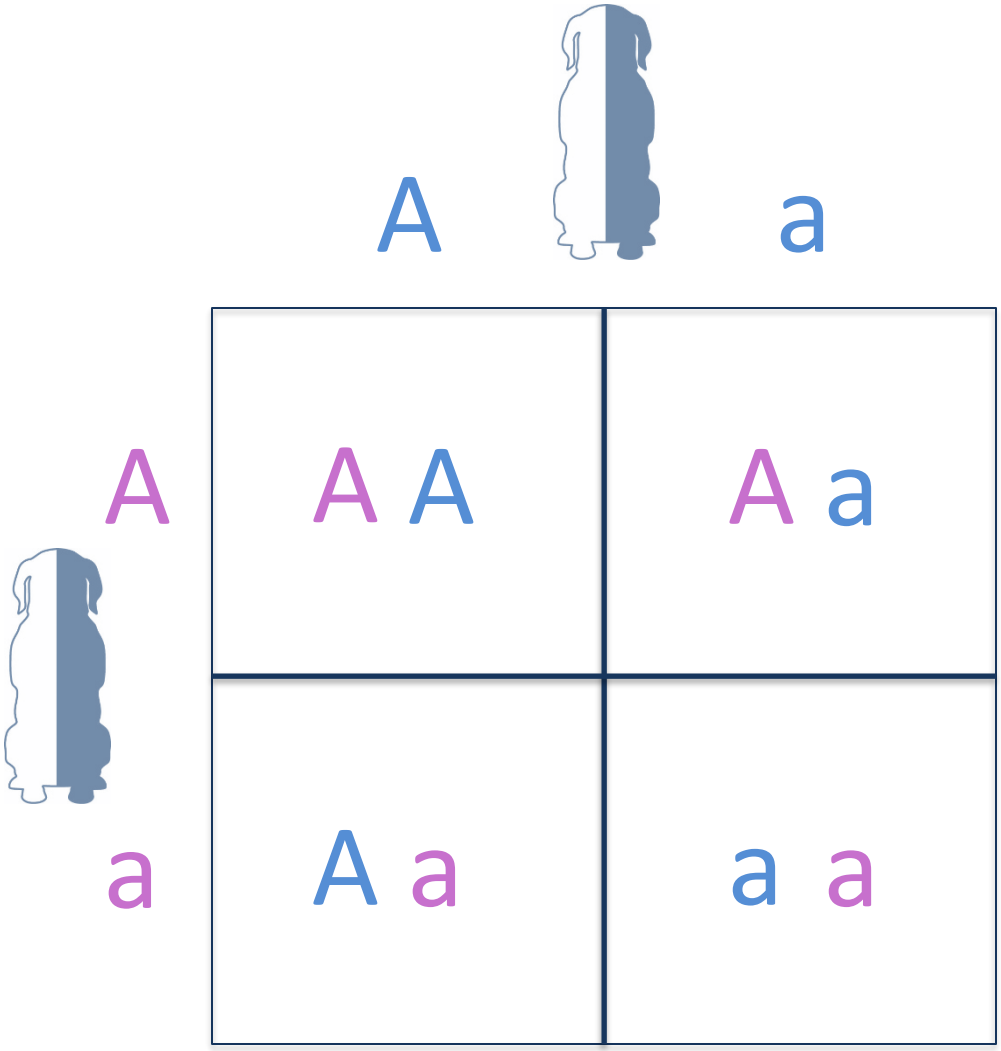
Inheritance Patterns: Recessive



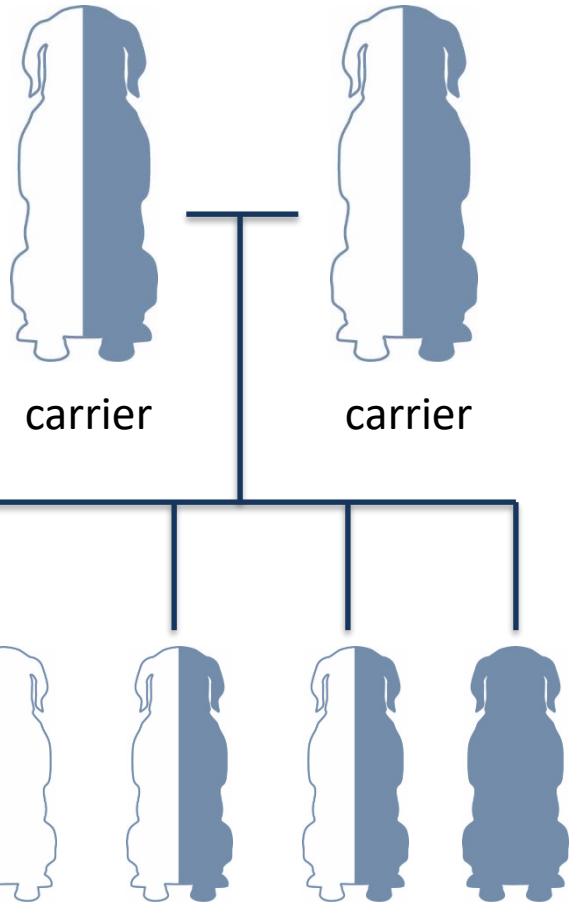
carrier carrier



25% normal AA | 50% carrier Aa | 25% affected aa



Inheritance Patterns: Recessive



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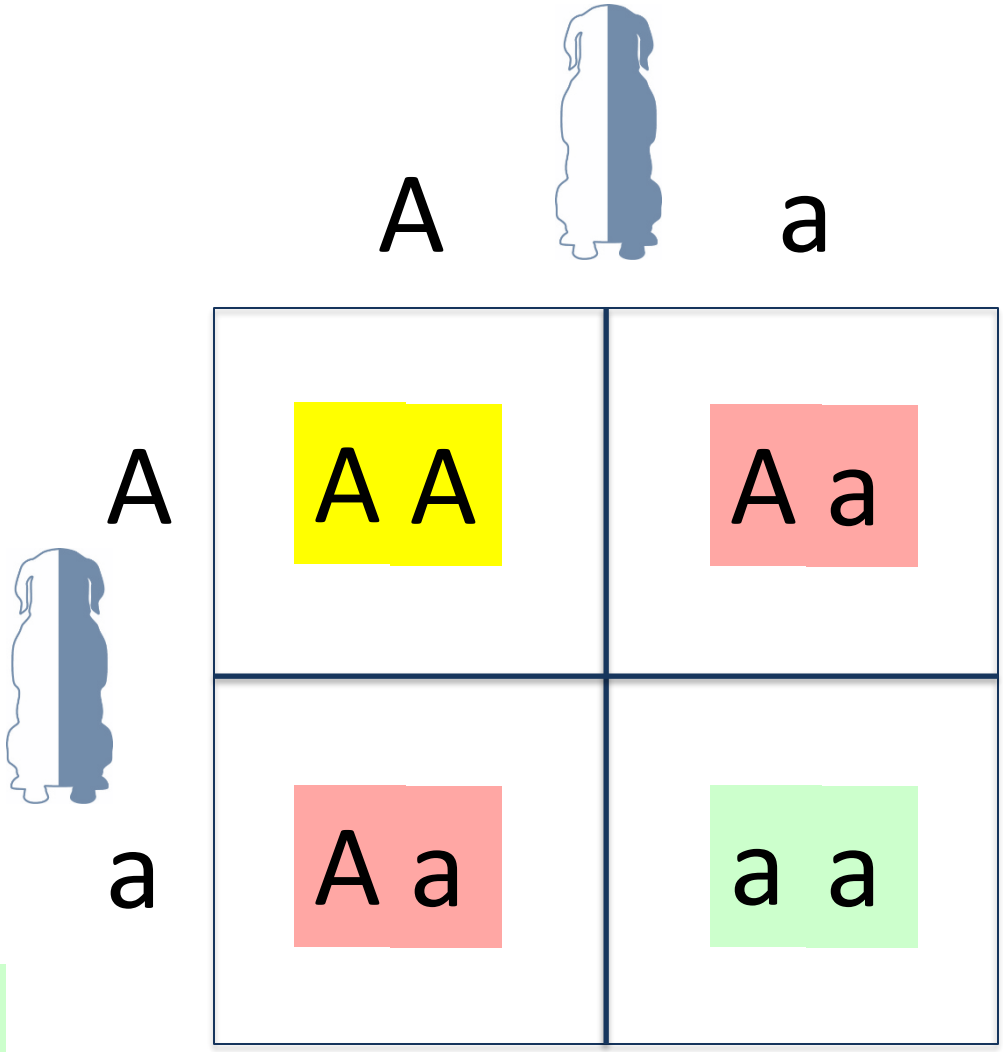

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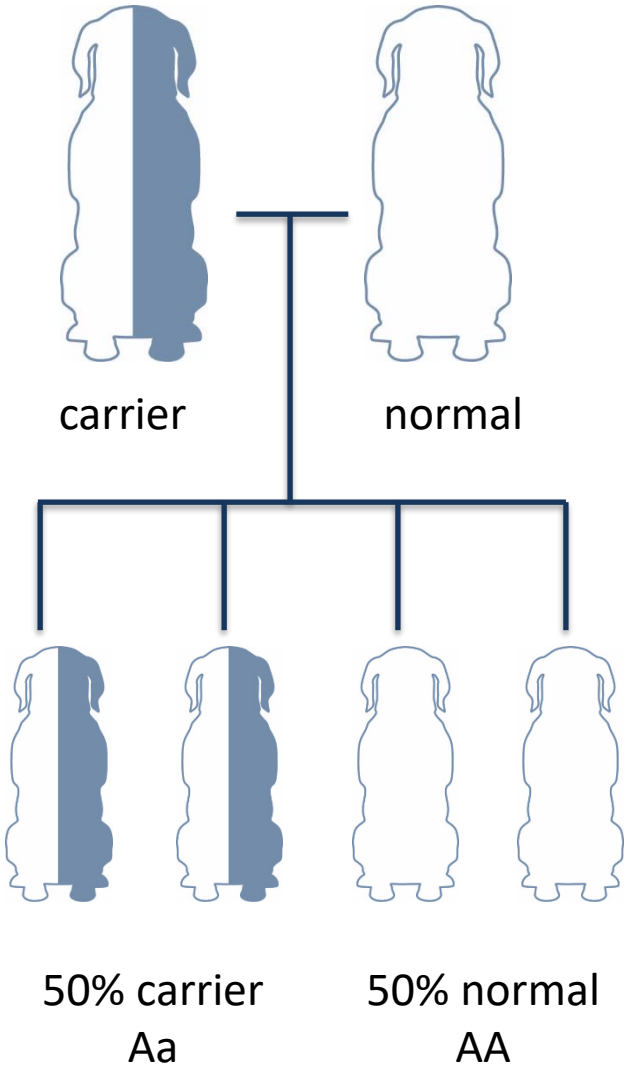

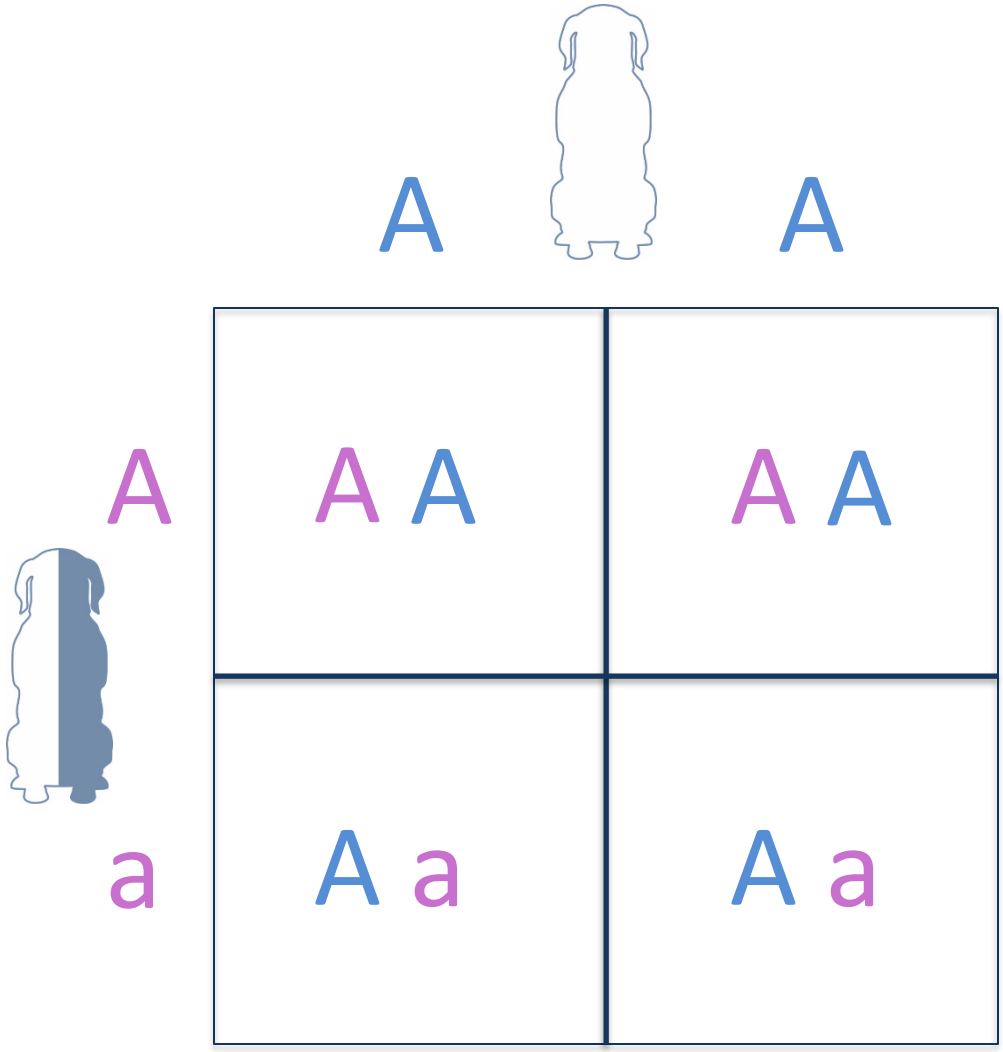

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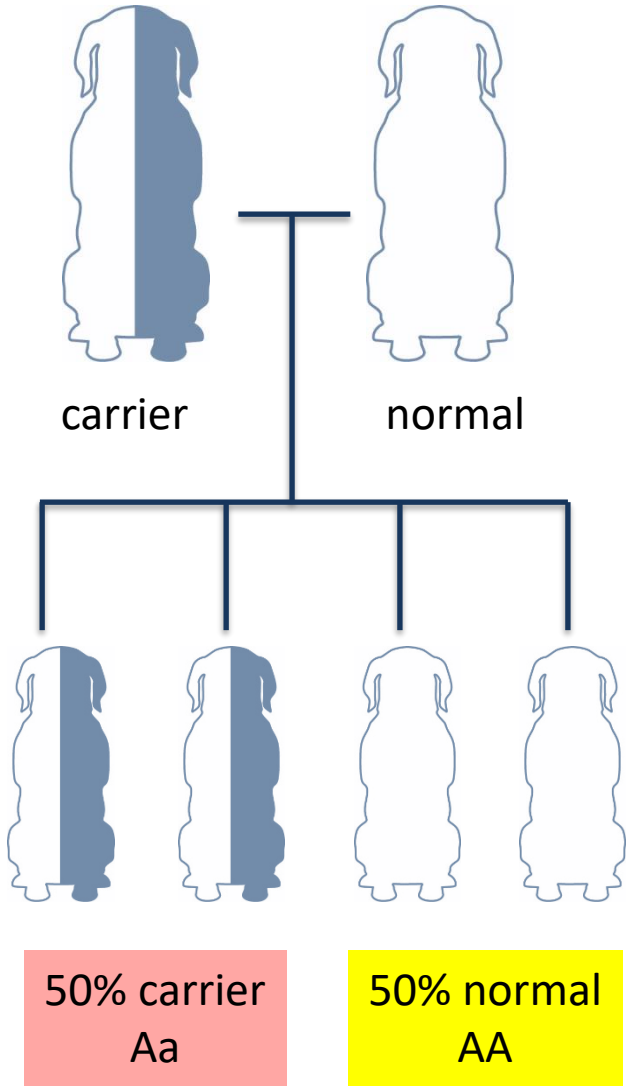

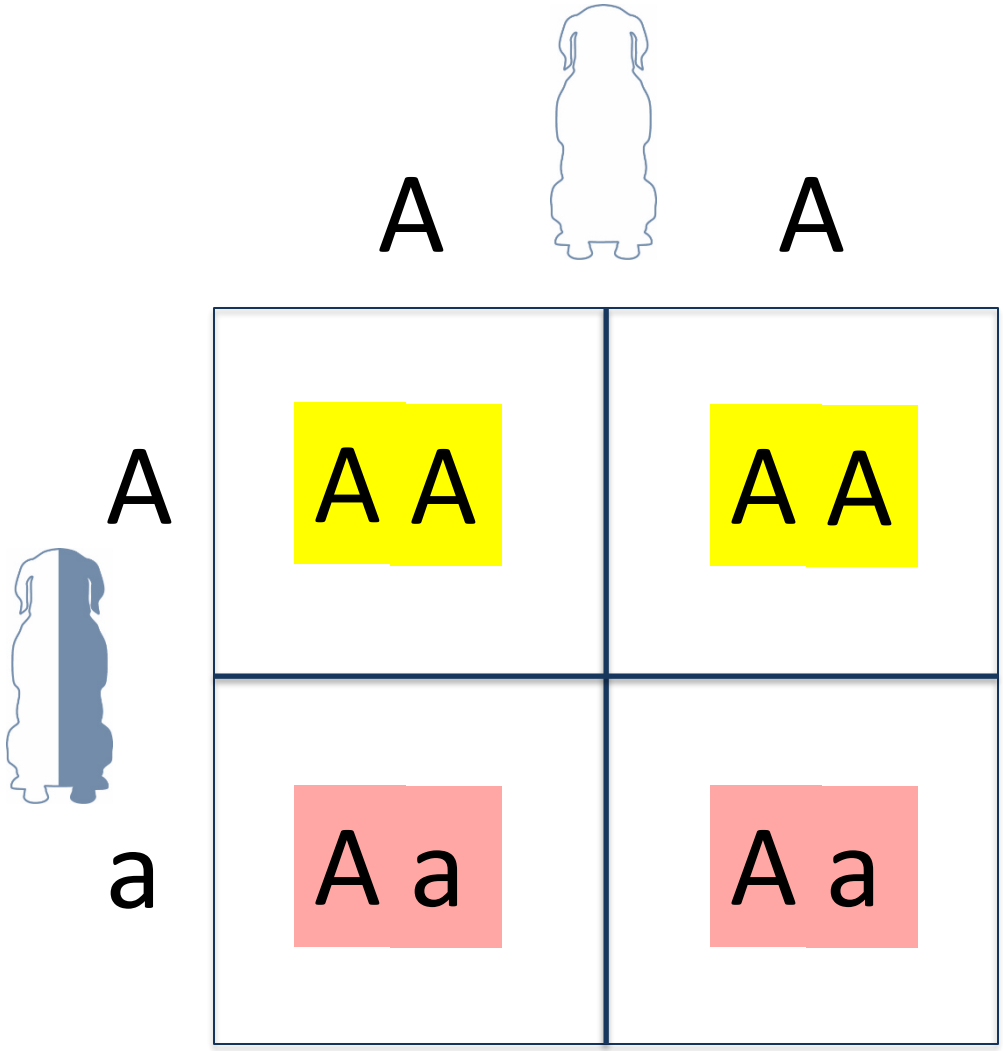

Collie Eye Anomaly

- *NHEJ1* Gene- Recessive with variable expressivity
- Congenital bilateral eye disease also known as choroidal hypoplasia (CH)
- May not be seen on eye exam after about 12 weeks of age in mild cases- "go normal"
- More common to be mildly affected than severely affected
- Common signs
  - Underdevelopment of choroid- Layer of eye supplying blood and nutrients
  - Focal lack of pigmentation in retina
  - Abnormal blood vessels
  - Coloboma of optic disc
  - Retinal folds
  - Bleeding in eye
  - Detached retina
  - Vision deficits or blindness

Degenerative Myelopathy

- *SOD1* gene- Recessive with incomplete penetrance
- Late-onset, progressive neurological disease- Average age of onset is 6 to 10 years of age.
- Common signs:
  - Hindlimb weakness- Trouble standing up and using stairs
  - Abnormal gait
  - Dragging hind toenails/feet and abnormal limb placement
  - Progresses over 6 months to 2 years to also include the front limbs and other neurological pathways
  - Dogs with end stage DM often develop incontinence and respiratory failure

Exercise-Induced Collapse

- *DNM1* gene- Recessive with variable expressivity
- Neurological disease resulting in collapsing episodes associated with exercise
- Common signs:
  - Wobbly, uncoordinated gait after 5 to 20 minutes of exercise. Often most obvious in hind end. May drag hind limbs for short time
  - Typically remain alert and are not in pain
  - Occasionally dogs may experience confusion, loss of consciousness, seizures, or in rare circumstances, death
  - Dogs typically recover within 30 minutes and are normal between episodes
  - Risk to dogs swimming or performing other activities

PRA- Cone-Rod Dystrophy 4

- *RPGRIP1* gene- Recessive with incomplete penetrance
- Degenerative retinal disease with wide age of onset range- Reported from 1 to 15 years of age.
- Variable progression rate
- Common signs:
  - Vision deficits up to complete blindness
  - Significant variation in age of onset and progression

Boykin Spaniel Panel

- How common are the mutations tested for in the Boykin Spaniel Panel?
- We don't know the specific frequency or distribution of these mutations in the general Boykin population
- PPG test results (as of 8/17/20):

	Carrier	At risk/Affected
Collie Eye Anomaly	41.6%	4.2%
Degenerative Myelopathy	22.2%	1.1%
Exercise-Induced Collapse	21.8%	1.2%
Progressive Cone-Rod Dystrophy 4	3.4%	None

Inheritance Patterns

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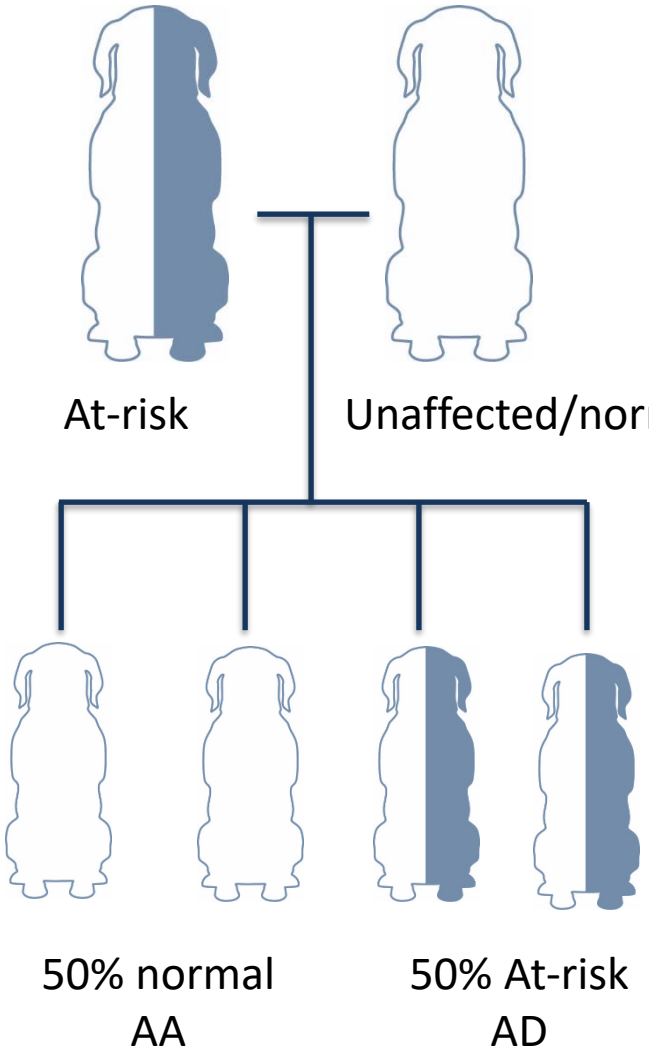
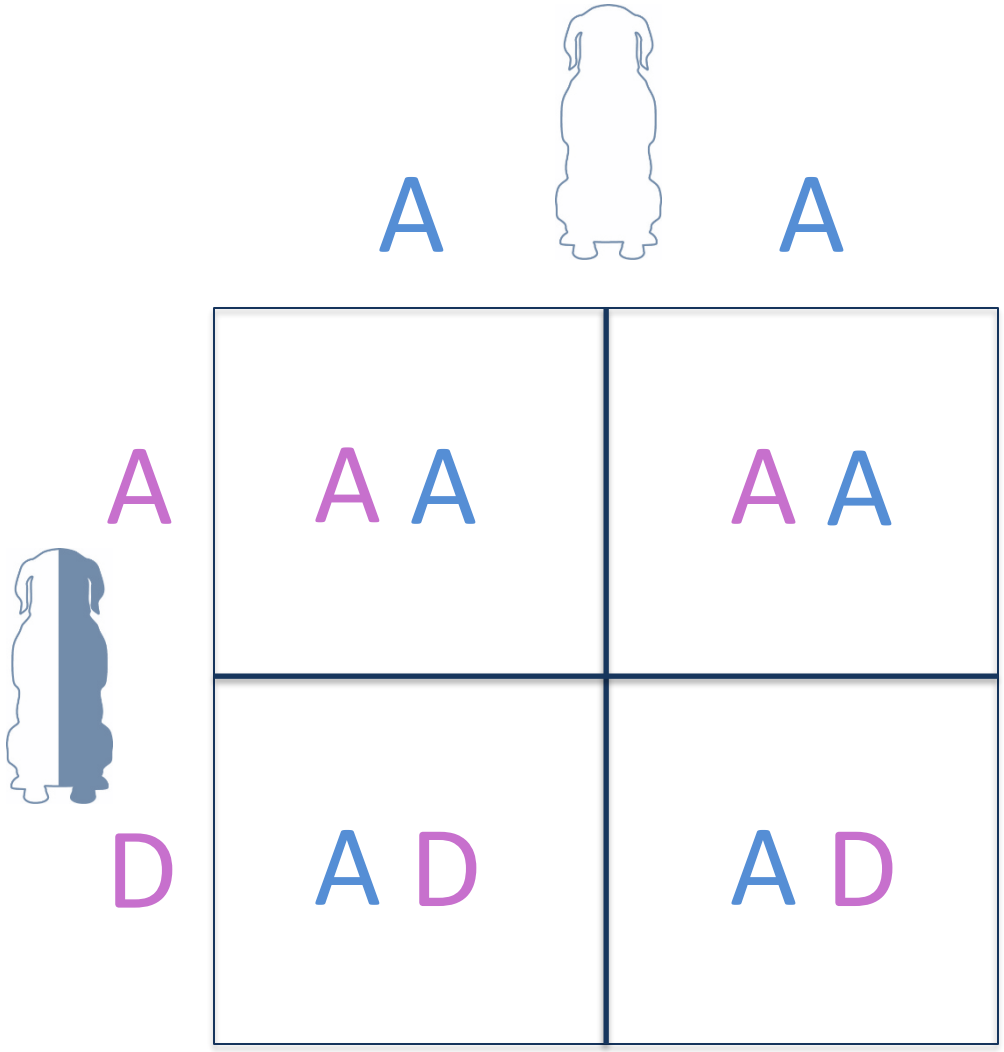
Inheritance Patterns: Dominant

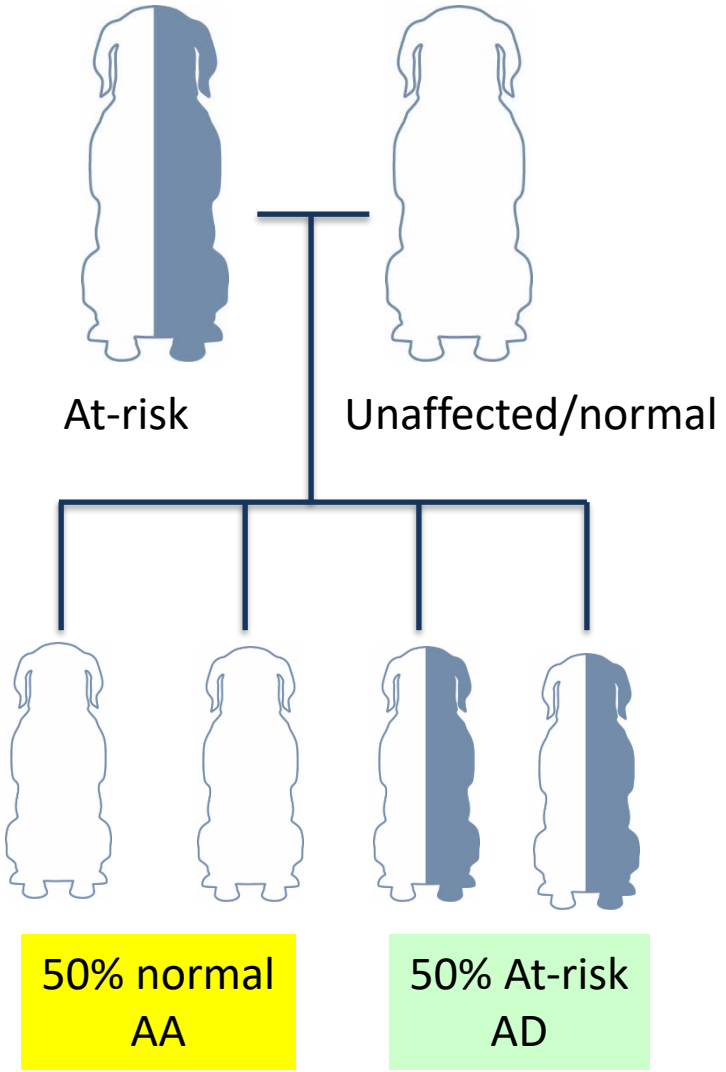
- Dominant diseases- only one copy of the associated genetic variant needed to develop the disease or increase risk of disease

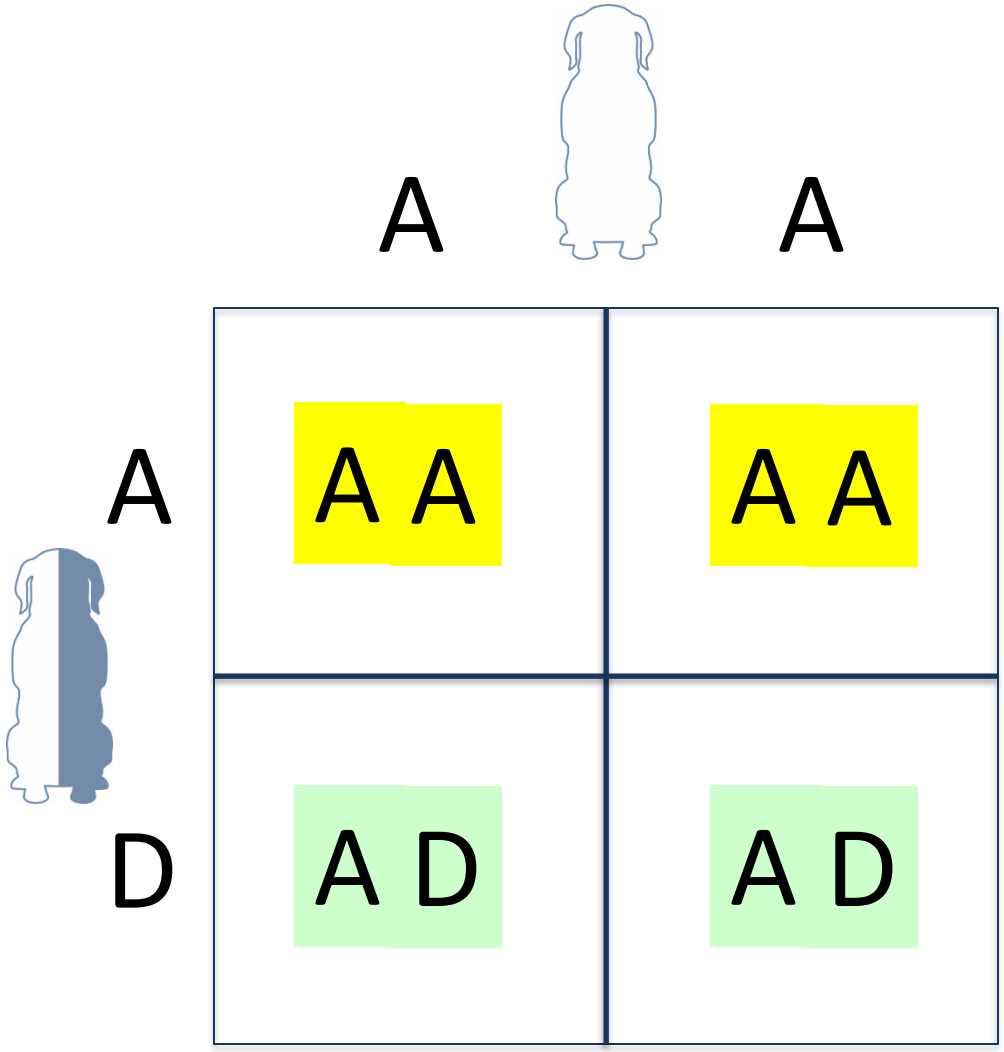
Inheritance Patterns: Dominant





Inheritance Patterns: Dominant





CDDY, CDPA, and IVDD

- Two known genetic mutations associated with shortened limbs in dogs
- A portion of the *FGF4* gene has been duplicated and inserted in two aberrant locations; one on chromosome 12 (CFA12) and one on chromosome 18 (CFA18)
- Dogs inheriting the CFA12 mutation display shorter limbs due to chondrodystrophy (CDDY), and approximately 5 to 15 times increased risk of IVDD Type I
- Dogs inheriting the CFA18 mutation display shorter limbs due to chondrodysplasia (CDPA), but are not at an increased risk of IVDD

FGF4 Gene-Chr. 18

Chr. 18- Chondrodysplasia (CDPA)

Chr. 12- IVDD risk/ Chondrodystrophy (CDDY)

CDDY, CDPA, and IVDD

- Type II IVDD- Age related type of IVDD
  - Age related changes to IVDs
  - Older dogs- >6 years common
  - Bulging/herniation into spinal cord
  - Acute flare ups on chronic disease
  - Pain, neurological dysfunction, weakness
  - Surgery rarely indicated
- Type I IVDD-
  - Associated with CFA12 *FGF4* insertion
  - IVD degeneration begins before one year of age
  - Younger Dogs- 3 to 7 years common
  - Calcification of nucleus pulposus and replacement with chondrocytes
  - Progressive weakening of annulus fibrosus
  - Violent herniations into spinal cord
  - Severe acute pain, neurological dysfunction, weakness, paralysis
  - Surgery often indicated

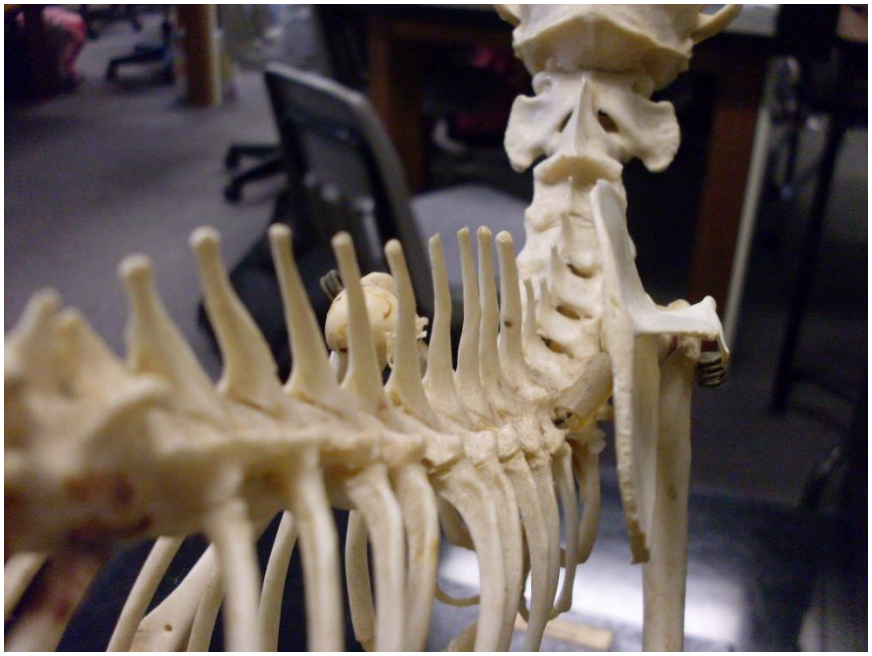
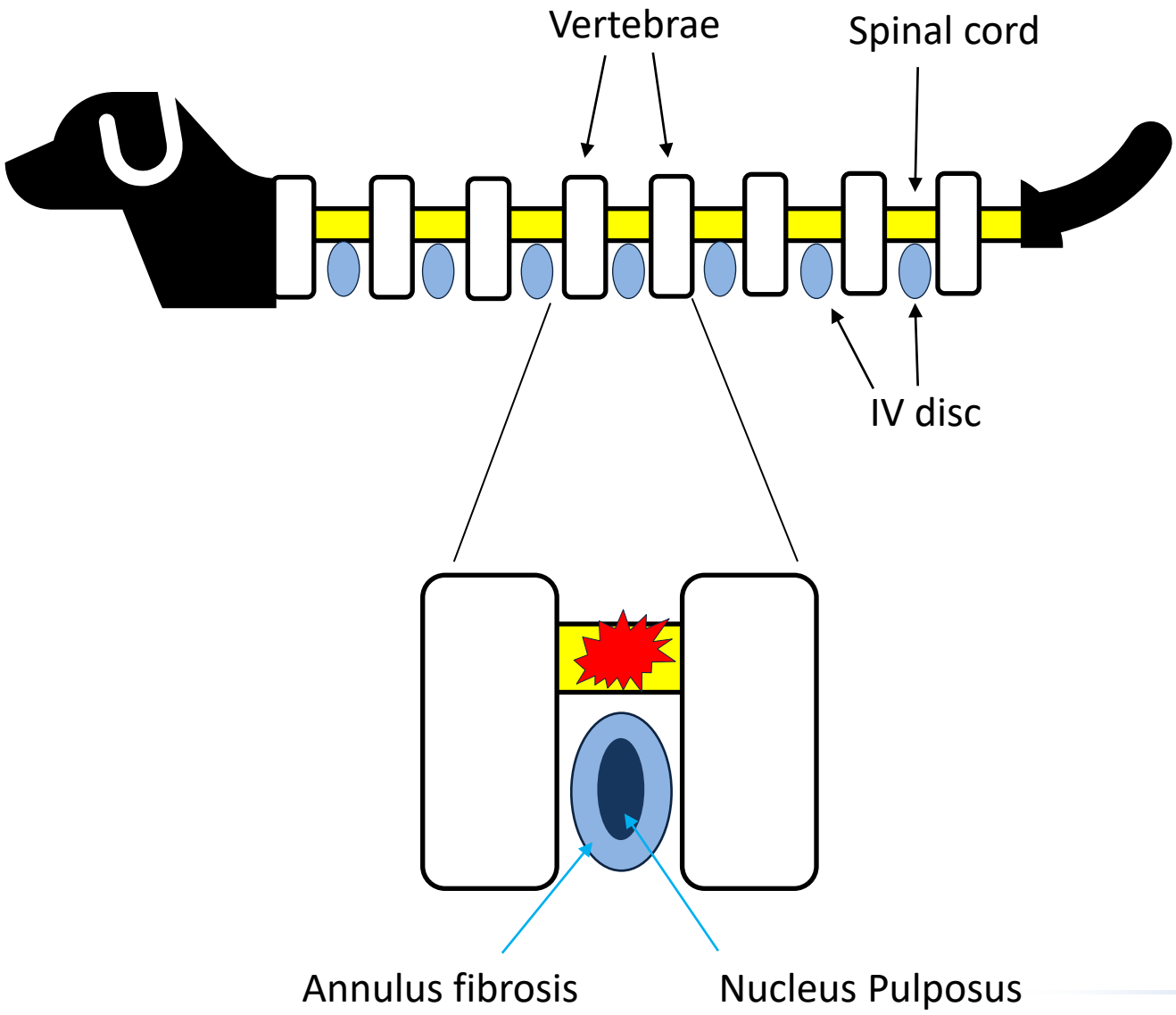


*Photo courtesy of Dallas Krentzel via Flickr Creative Commons license

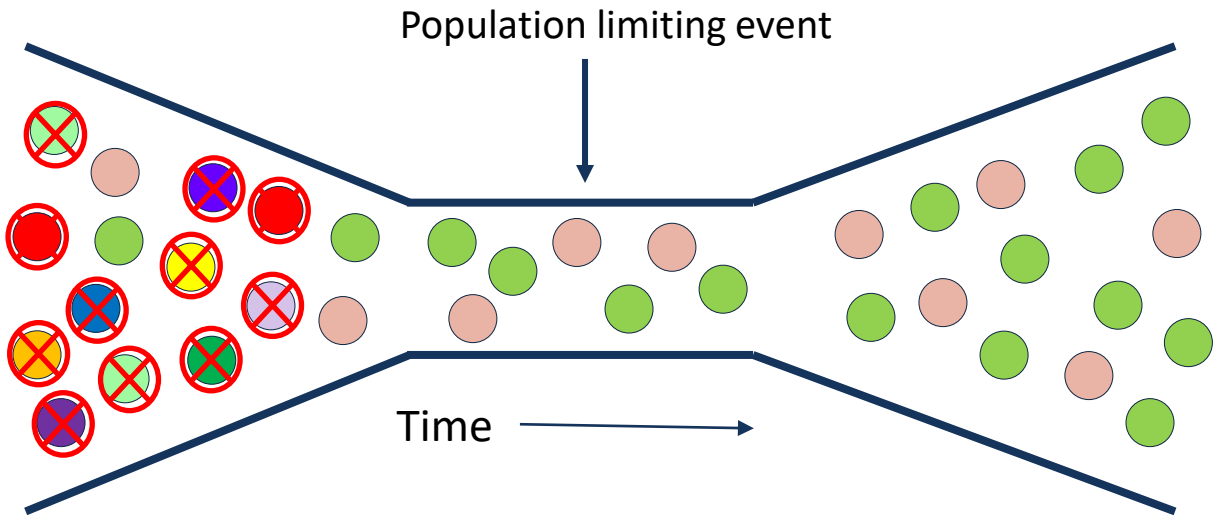
CDDY, CDPA, IVDD



CDDY, CDPA, and IVDD

- Breeding to avoid IVDD must address two issues:
  - Potential loss of genetic diversity
  - Meeting breed standard leg length

Genetic Bottleneck- Diversity Loss



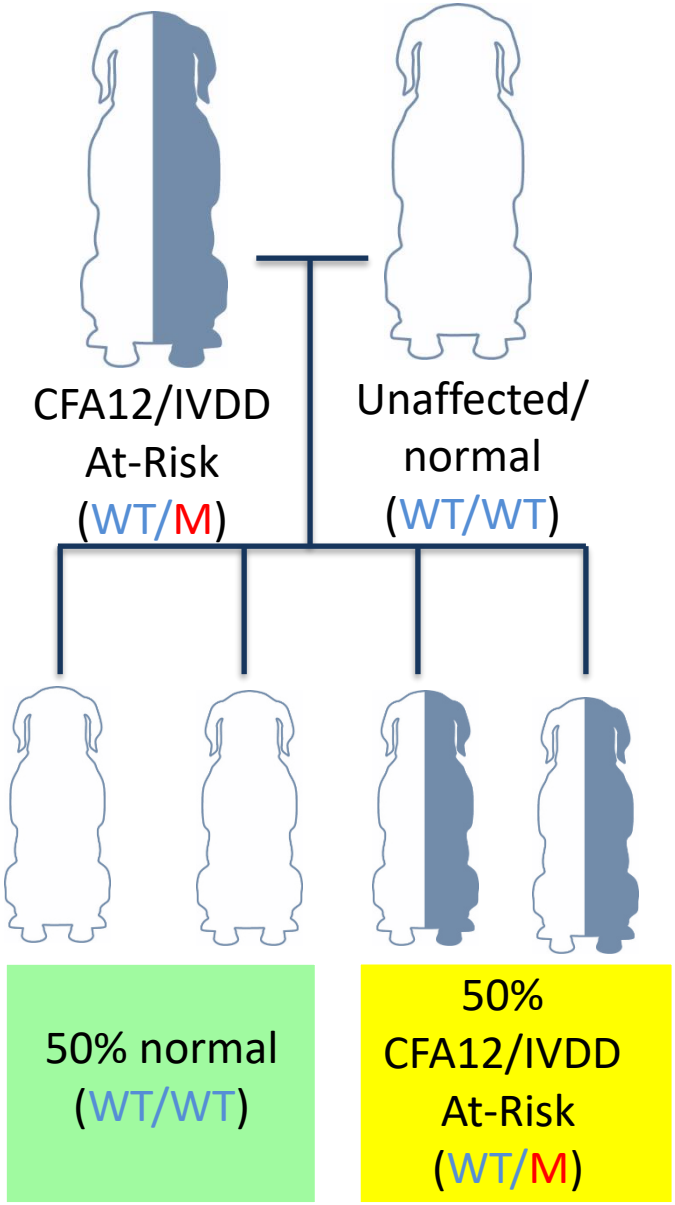
- Dogs are excluded from breeding- Same effect as them dying before reproducing
- Population is repopulated with limited number of dogs→Less genetically diverse population
- New population more closely related and more likely to share the same disease-associated recessive mutations
- Potential for increase in MANY OTHER recessive diseases, shortened lifespan, decreased litter sizes

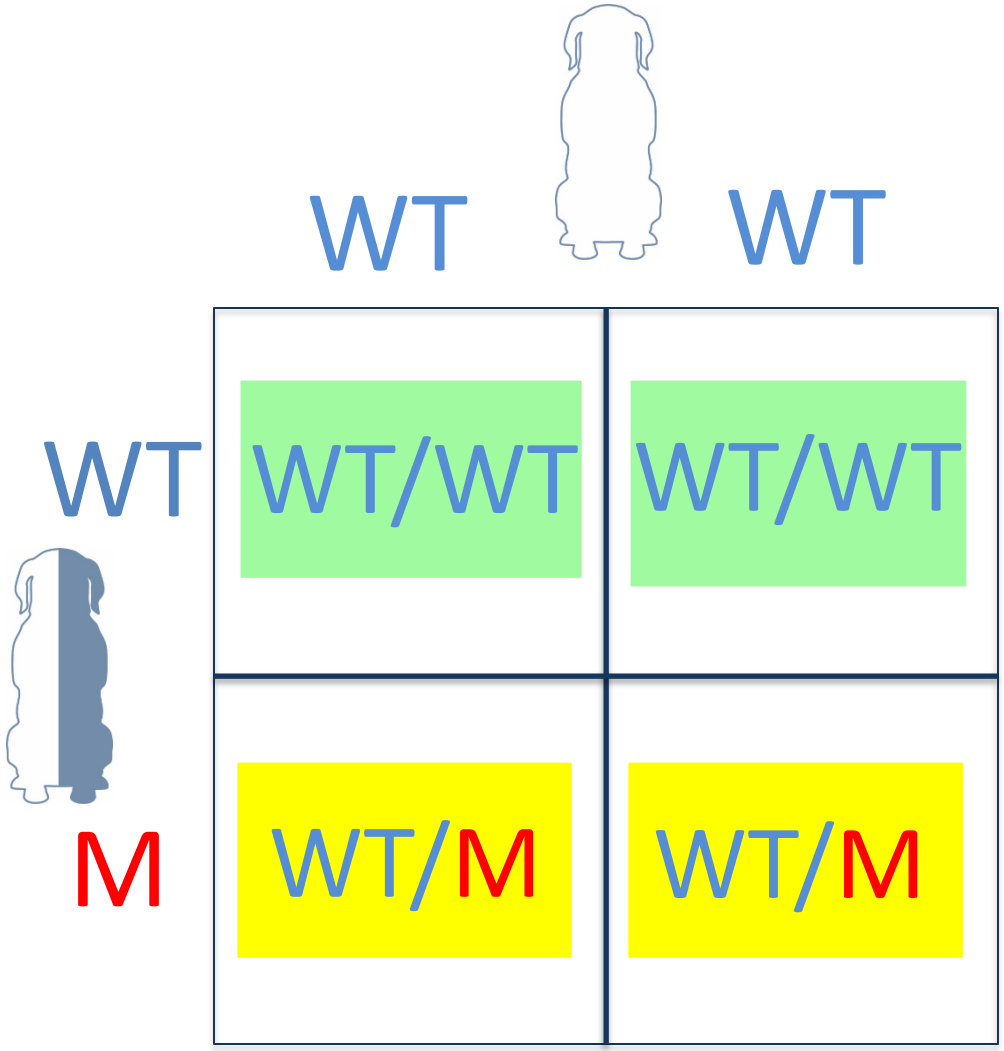
Breeding Strategies- CDDY/IVDD

- Frequency of each mutation varies from breed to breed-
  - On average, each Boykin spaniel carries one copy of CFA12 insertion*
- Slow removal of CFA12 insertion over a few generations would be preferable in most cases
  - Dogs with 1 copy of CFA12 insertion could be bred to dogs that are clear of the CFA12 insertion- 50% clear pups
  - If a clear dog cannot be found, may need to breed to other CFA12 carriers to start getting clear dogs- 25% clear pups, but 25% also have two copies of the mutation- Less desirable

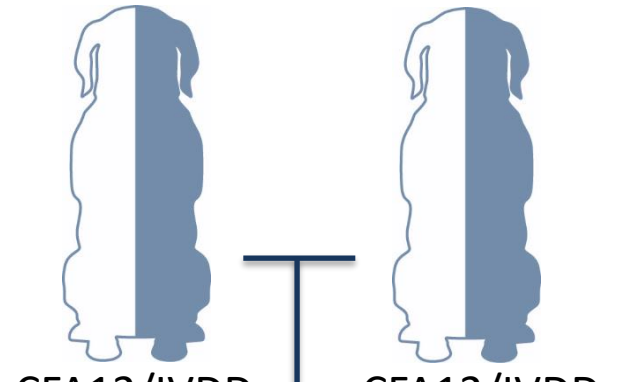
*UC Davis Veterinary Medicine Website- Chondrodystrophy (CDDY and IVDD Risk) and Chondrodysplasia (CDPA) statistics: https://vgl.ucdavis.edu/test/cddy-cdpa

IVDD- *FGF4* CFA12: Dominant





Inheritance Patterns: Dominant



CFA12/IVDD
At-Risk
(WT/M)

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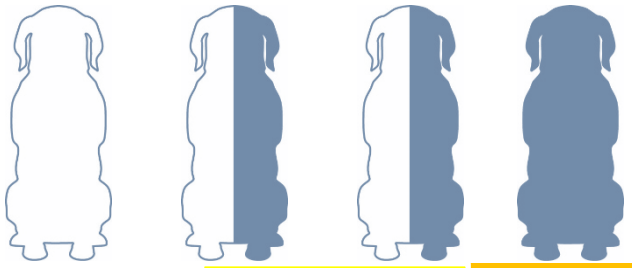
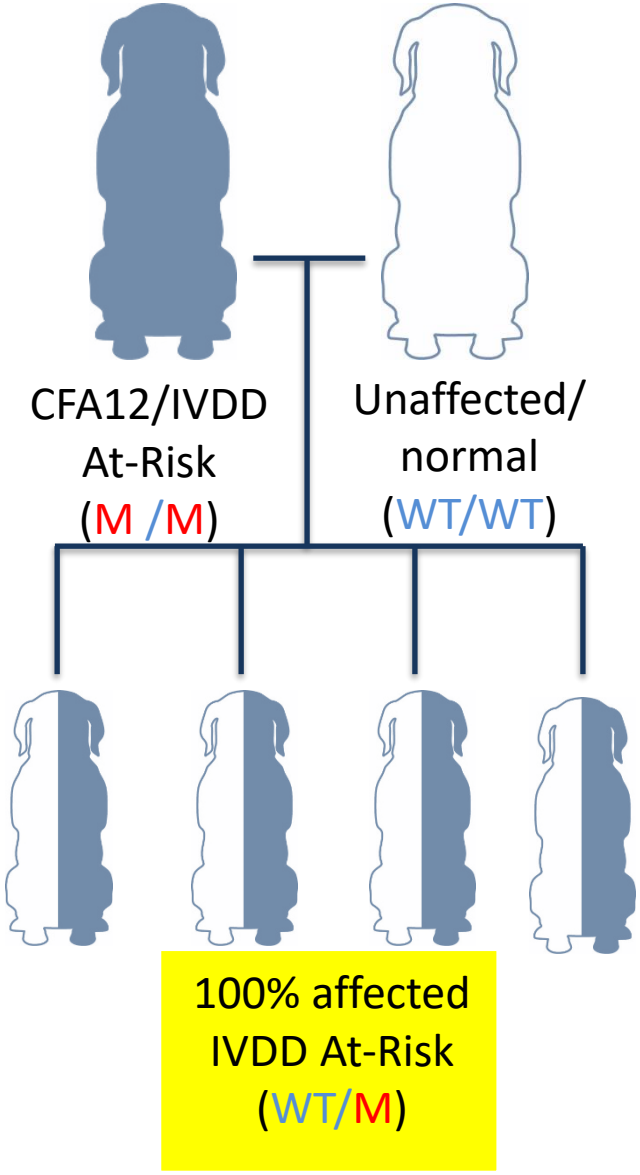
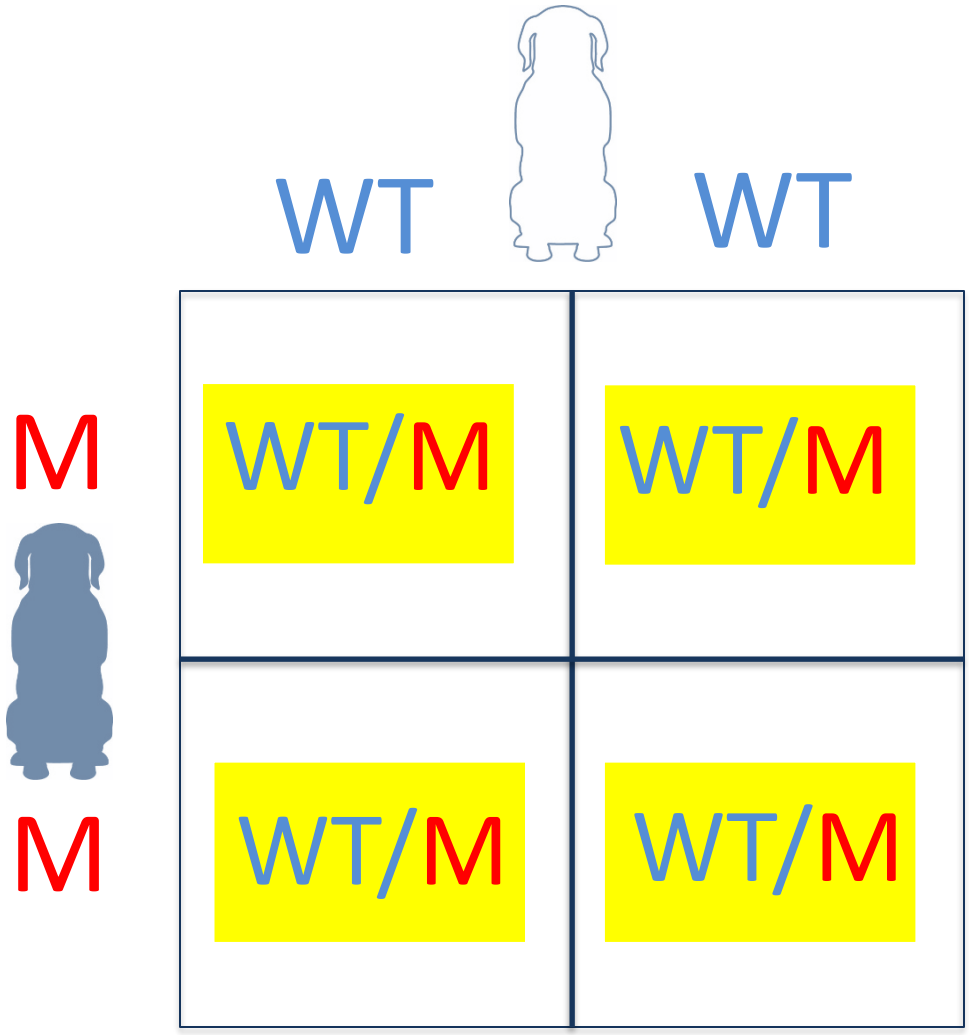


25% normal (WT/WT)	50% CFA12/IVDD At-Risk (WT/M)	25% CFA12/IVDD At-risk (M/M)

	WT	M
WT	WT/WT	WT/M
M	WT/M	M/M

IVDD- *FGF4* CFA12: Dominant





Breeding Strategies- CDPA

- Increase in leg length associated with removal of the CFA12 mutation may be undesirable
- In some breeds, breeders may be able to breed away from the CFA12 (CDDY/IVDD) insertion and select for the CFA18 (CDPA) insertion:
  - Maintain shortened legs
  - Reduce risk of IVDD
- CFA18 (CDPA)- No report of the mutation frequency in Boykin spaniels

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Questions?

Contact Casey at PPG

- Phone: 509-483-5950 (Mon. to Fri.; 8 am to 5 pm Pacific time)
- Email: ccarl@pawprintgenetics.com
- Facebook: https://www.facebook.com/caseyat.ppg

Thank you for inviting me!