



Testing for Canine Genetic Diseases

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UCDAVIS

VETERINARY MEDICINE

Outline

- Background on dog breeds and inherited diseases
- Basic genetics: The Rules
- Not so basic genetics: The exceptions to the Rules
- DNA tests

Breed Definition

- A breed is a "relatively homogeneous group of animals within a species, developed and maintained by man."
- This is not based on DNA or genetics

Limited Gene Pool



- There are limited numbers of dogs that founded each breed.
- “New” blood is very difficult to add once a breed is registered (example at end).
- In the past, location could also restrict use of sires and further limit the gene pool.

Popular sire

- Shipped and frozen semen
- No limits on number of offspring produced by one sire.
- The top winning dog is the one that everyone wants to use whether it is the winner of Westminster KC or the national specialty winner.
- This results in inappropriately large contributions from few individuals to the gene pool



Inbreeding



- Inbreeding means breeding related dogs
- Uncovers recessive traits or diseases
 - These can be desirable or undesirable.
- Can lead to loss of diversity
- It is illegal in most states!

Dog breeds



Genetic Material- DNA

- Organized into chromosomes: long stretches of DNA
- Dogs have 38 pairs of chromosomes and 2 sex chromosomes.



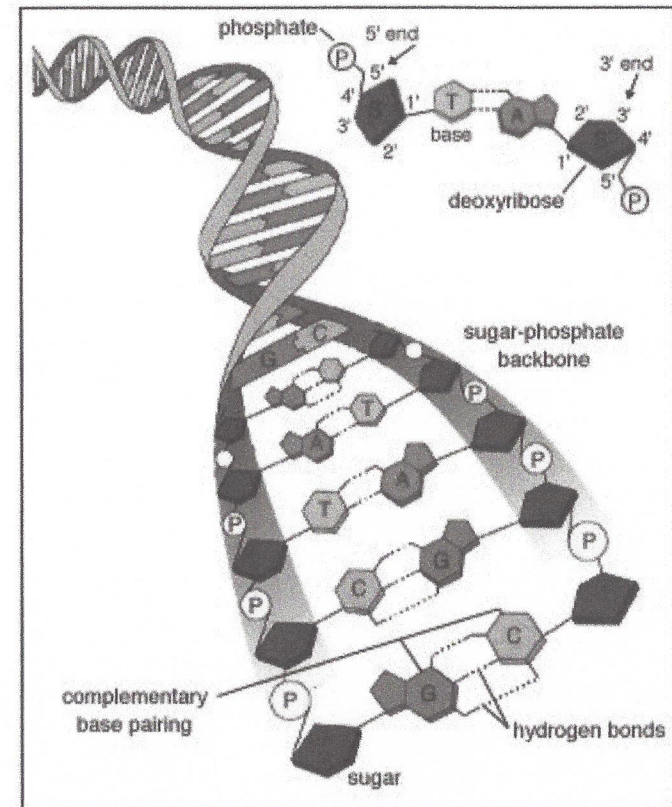
Image credit: Zentrum für Humangenetik Bremen
Universität Bremen

Provides the blueprint for life



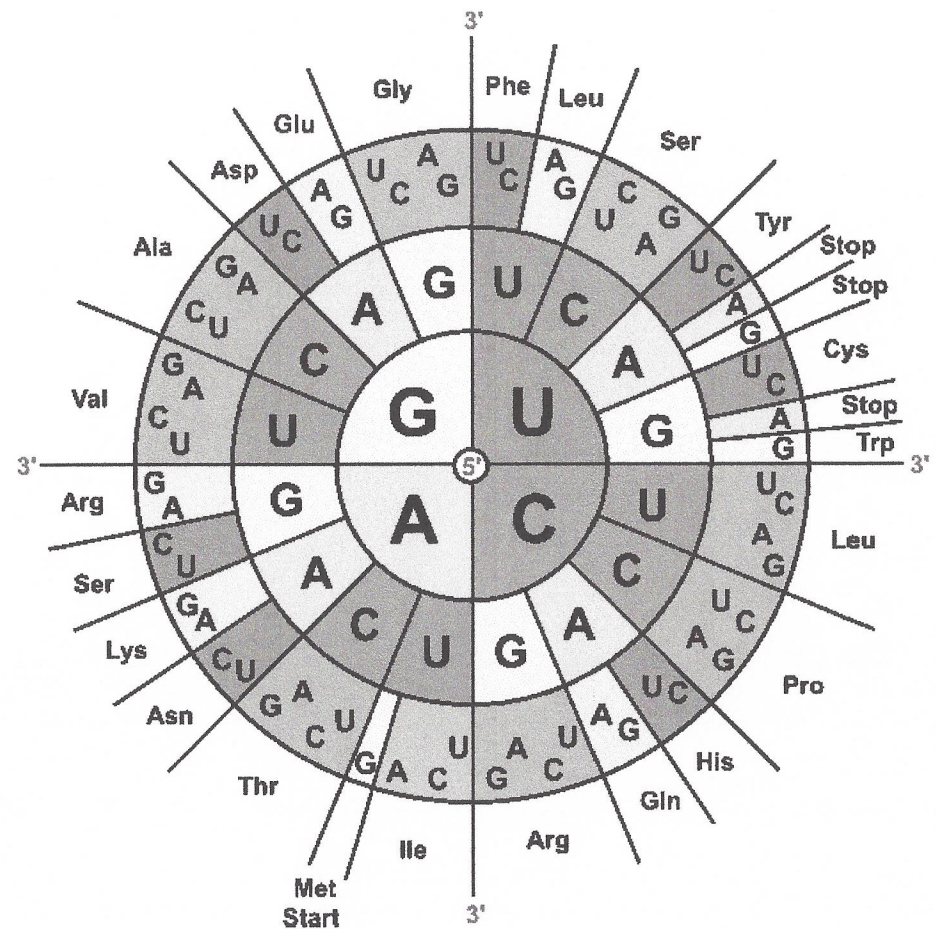
DNA sequence

- The sequence or order of bases of DNA codes for different proteins that provide all the tools that cells and tissues need to perform their functions.



Mutations are changes in DNA sequence

- Proteins are string of amino acids coded for by the DNA sequence.
- Changes in the DNA sequence lead to protein differences either in amino acid sequence or in where and when and how much of the protein is made.



Chromosome inheritance

- In order for the puppies to have two copies of every chromosome the sire and dam pass one of their chromosomes to each puppy.

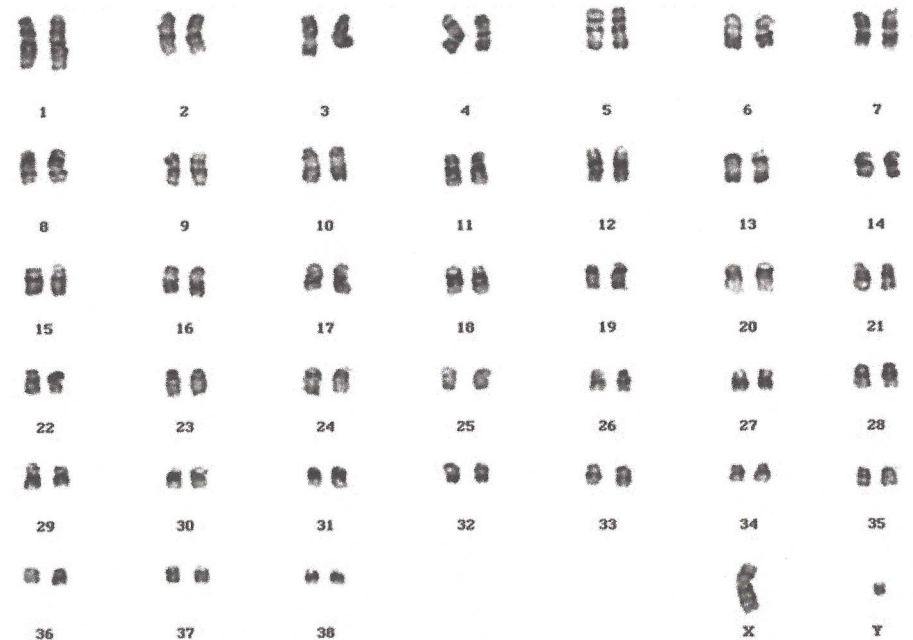
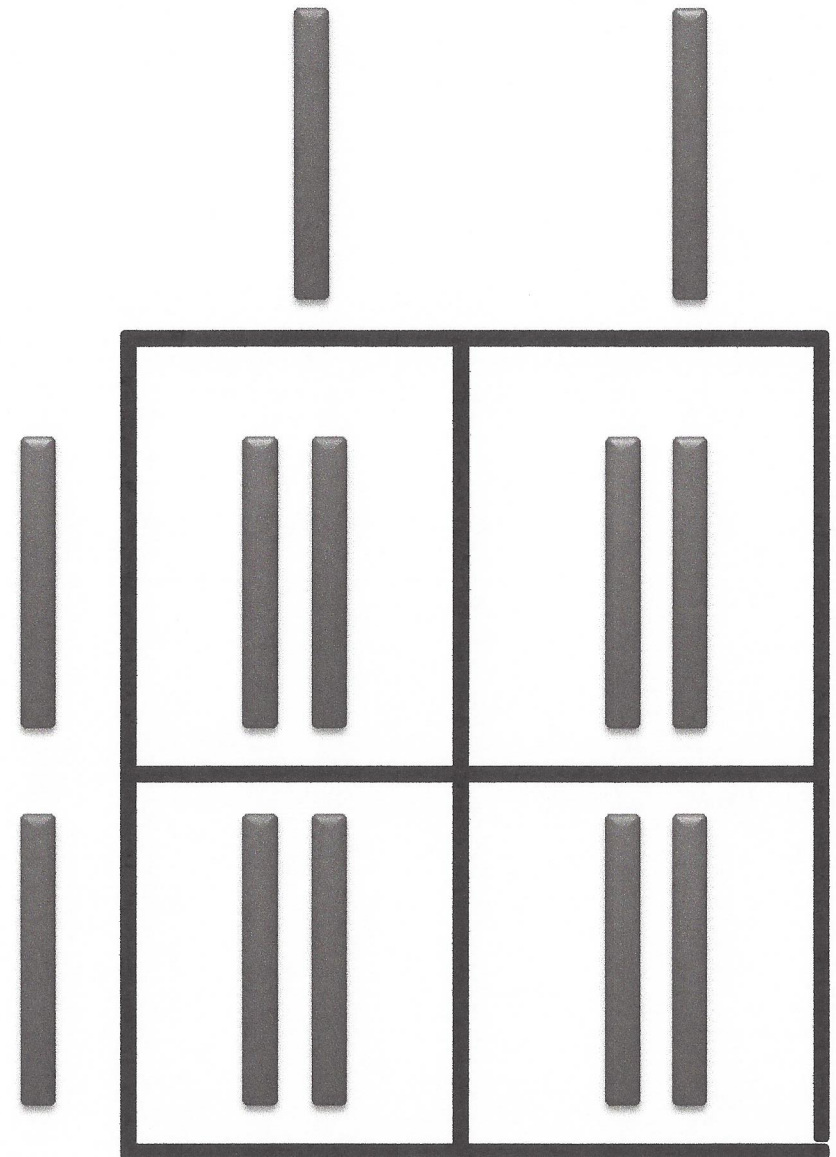
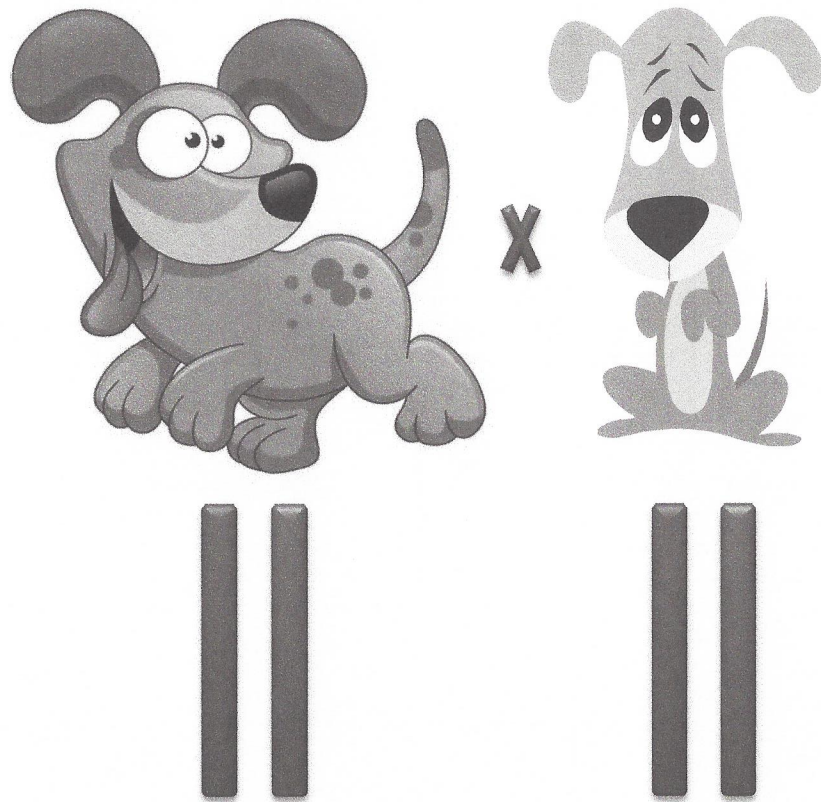
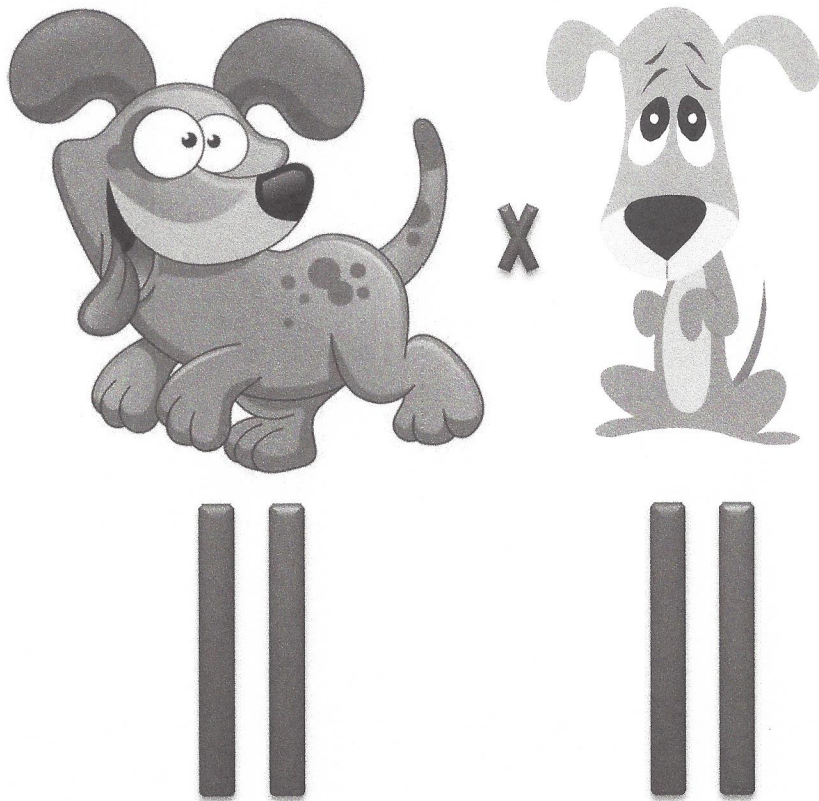


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Universität Bremen

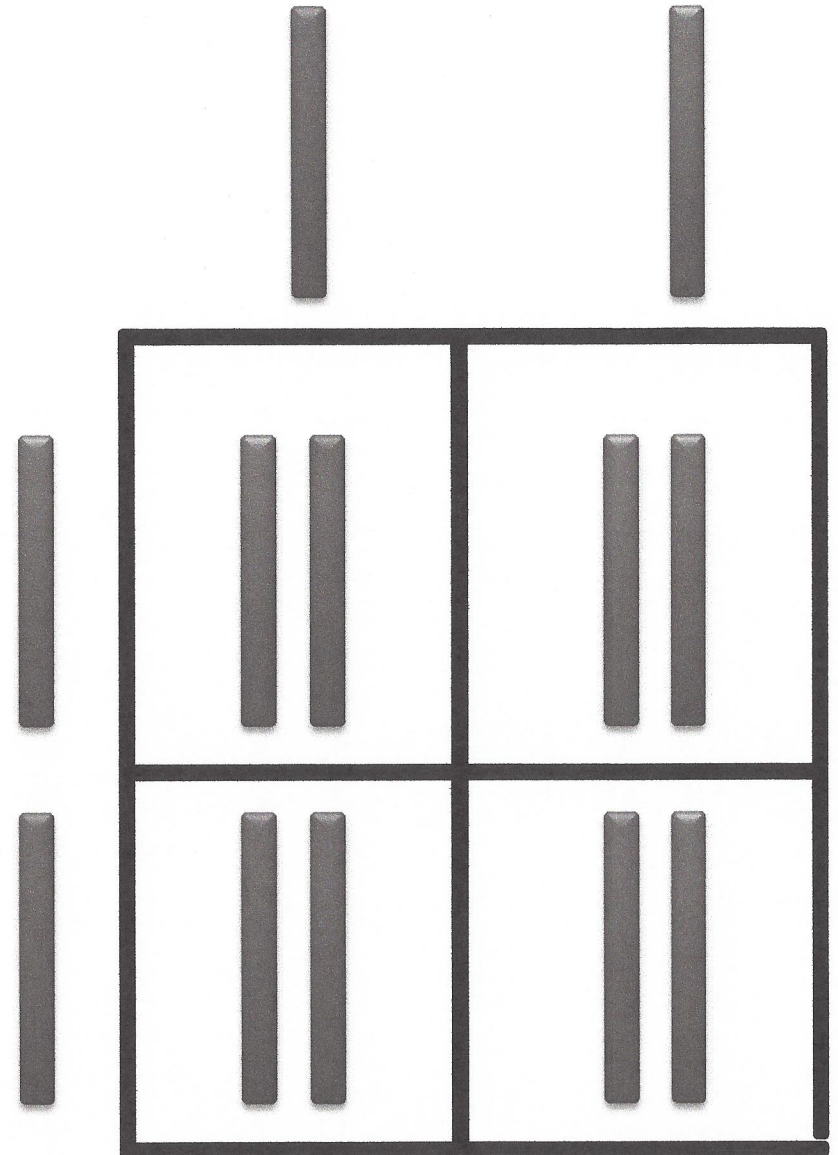
Segregation



Segregation

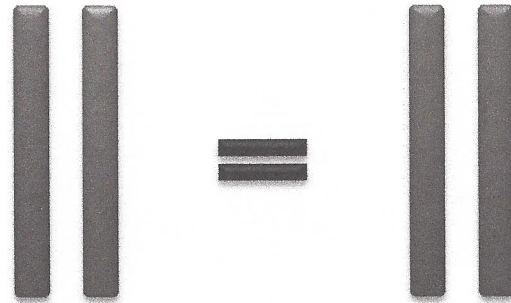


The cross of two heterozygotes produces 25% wildtype, 25% mutant and 50% carriers



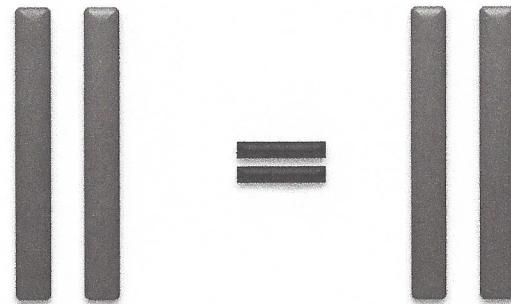
Phenotype

Dominant



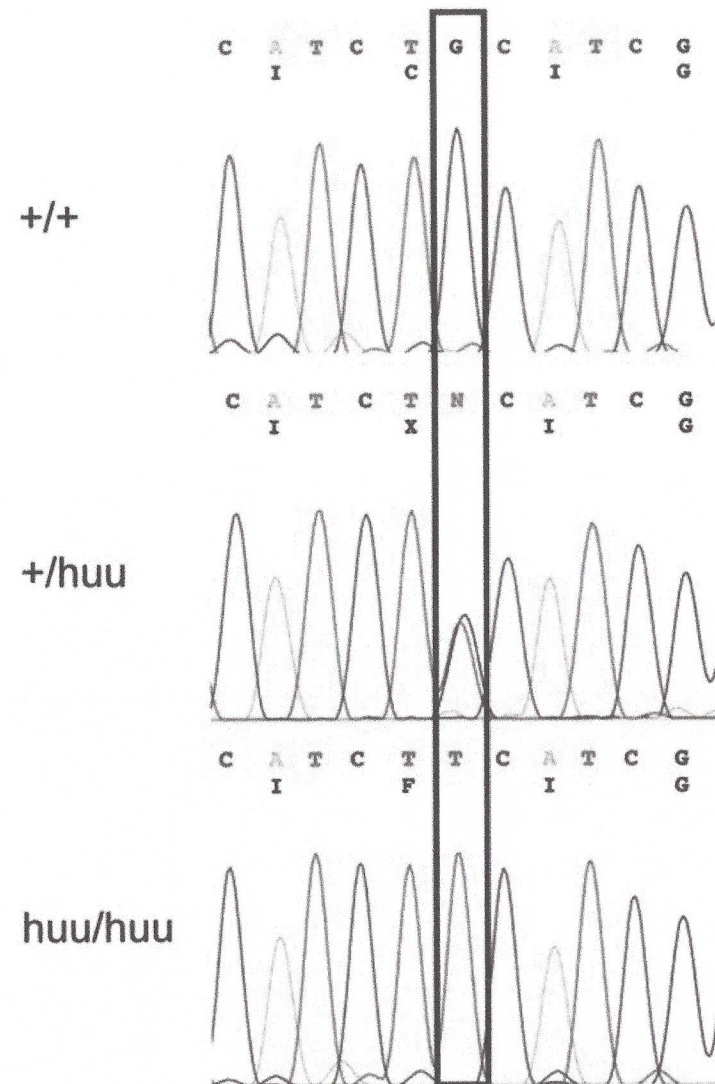
Or

recessive



Disease-causing alleles are changes in the sequence of the DNA

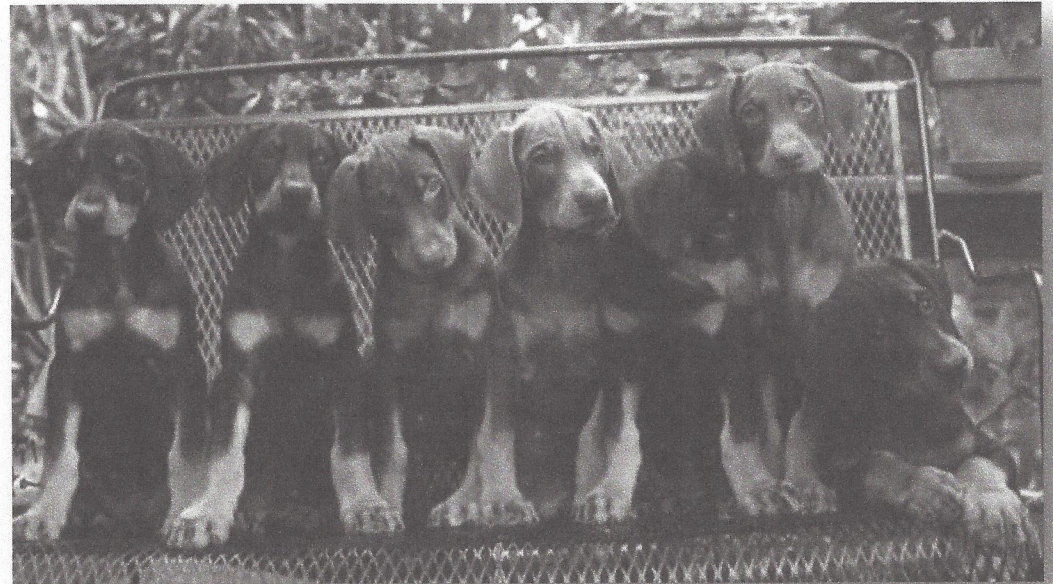
- Those changes in DNA can be insertions, deletions, or changes of a single base pair of DNA.
- Sometimes they can be large rearrangements of DNA or chromosomes.



Modes of inheritance

- Recessive: must have two copies of the mutation to see the disease or trait. When two carriers are bred 25% of the puppies will show the disease or trait and 50% will be carriers.
- Dominant: ONLY one copy is necessary to show the disease. When an affected dog is bred 50% of the offspring will be affected.

Recessive



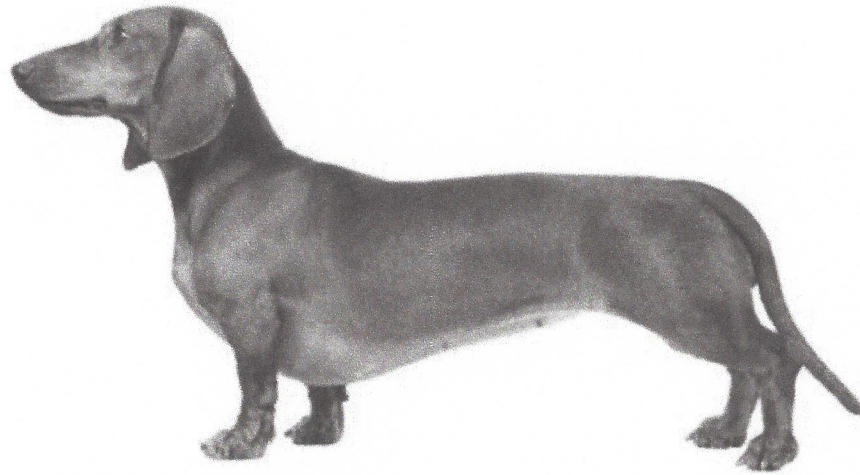
A noncoding melanophilin gene (MLPH) SNP at the splice donor of exon 1 represents a candidate causal mutation for coat color dilution in dogs.

Drögemüller C, Philipp U, Haase B, Günzel-Apel AR, Leeb T.
J Hered. 2007;98(5):468-73. Epub 2007 May 22.

Dominant



- Mutation in R-spondin-2 gene that increased the expression of the gene to three times the normal levels.



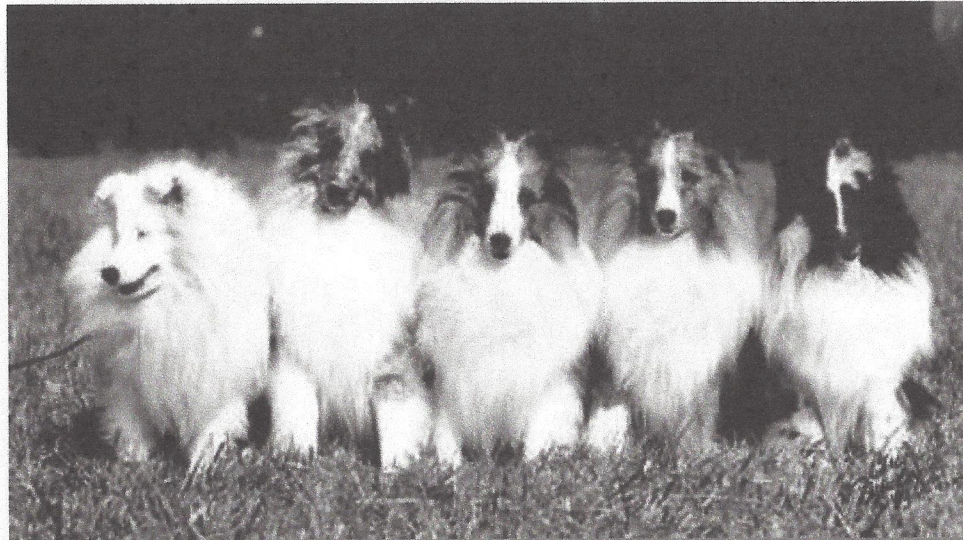
Coat Variation in the Domestic Dog Is Governed by Variants in Three Genes

Edouard Cadieu,¹ Mark W. Neff,² Pascale Quignon,¹ Kari Walsh,² Kevin Chase,³ Heidi G. Parker,¹ Bridgett M. VonHoldt,⁴ Alison Rhue,² Adam Boyko,⁵ Alexandra Byers,¹ Aaron Wong,² Dana S. Mosher,¹ Abdel G. Elkahoul,¹ Tyrone C. Spady,¹ Catherine André,⁶ K. Gordon Lark,³ Michelle Cargill,^{7*} Carlos D. Bustamante,⁵ Robert K. Wayne,⁴ Elaine A. Ostrander^{1†}

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Semi-dominant/co-dominant

- One copy of the mutation is enough to show outward disease or trait but two copies show a more severe disease or trait.



🏠 > Current Issue > vol. 103 no. 5 > Leigh Anne Clark, 1376–1381

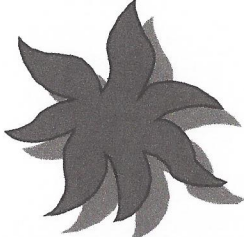
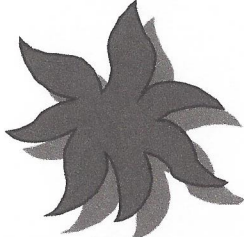
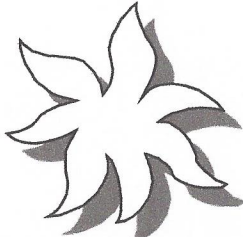
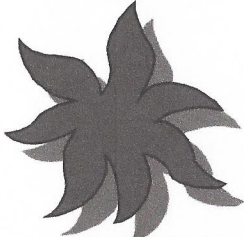
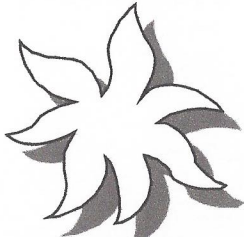
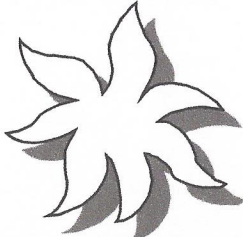
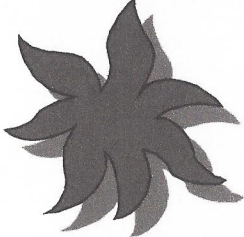
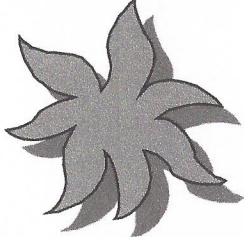
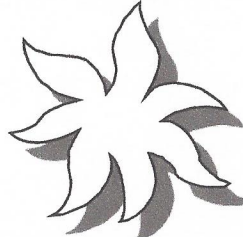
Retrotransposon insertion in *SILV* is responsible for merle patterning of the domestic dog

Leigh Anne Clark^{*†}, Jacquelyn M. Wahl^{*†}, Christine A. Rees[‡], and Keith E. Murphy^{*§}

Author Affiliations [✉]

Edited by Susan R. Wessler, University of Georgia, Athens, GA (received for review August 11, 2005)

Inheritance Models in Single Gene Trait

	Genotype Group		
Mode	AA	Aa	aa
A is Dominant			
A is Recessive			
A is Co-Dominant			

Beyond the basics- The exceptions

- Penetrance
- Expressivity
- Epistasis
- Risk/ susceptibility



Incomplete penetrance

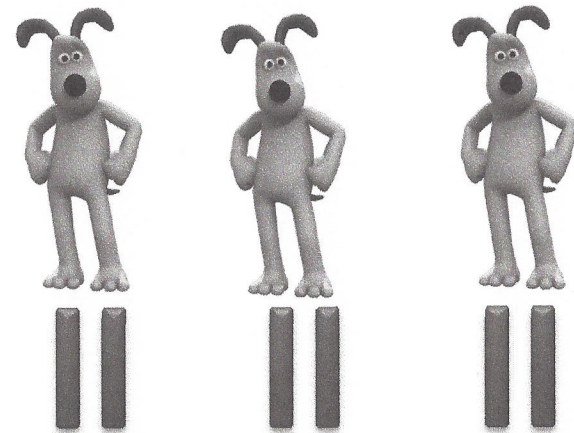
- The dog has the copies of the mutation required to be affected with the disease but it is unaffected.
- When you breed the dog it breeds as if it were affected.

Penetrance

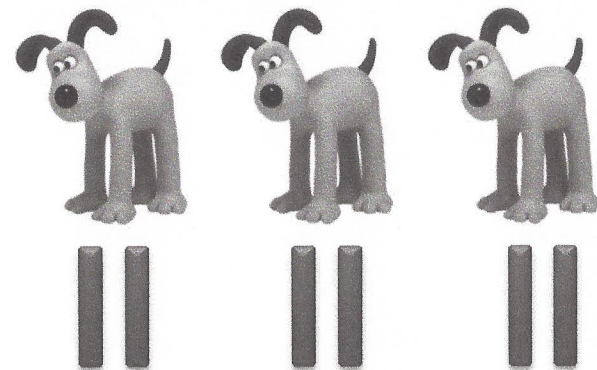
Example 50% penetrant

- Incomplete penetrance can be determined by pedigree analysis after the causative region or mutation has been identified.
- It is sometimes confused with a susceptibility mutation but they are different

Only these dogs get the disease

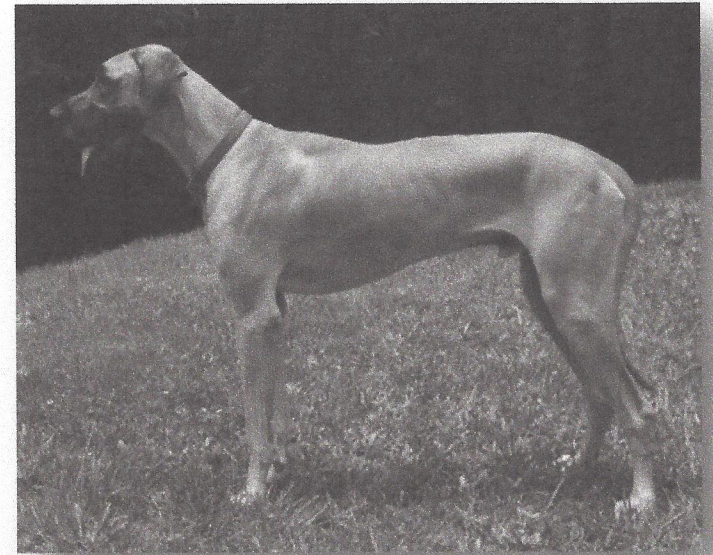


These dogs appear normal



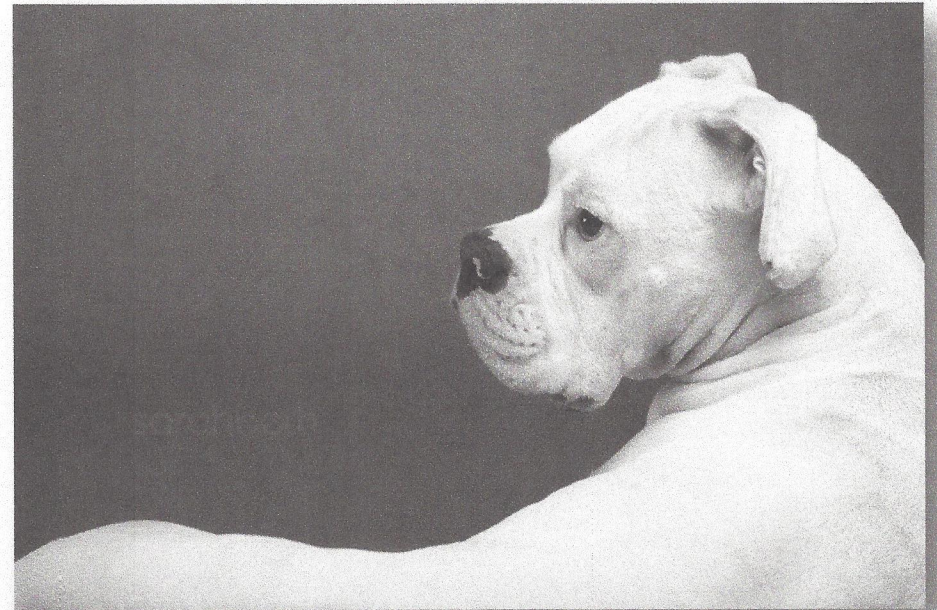
Expressivity

- Dogs with the same mutations may manifest the trait or the disease to different degrees.



Epistasis

- One mutation may mask the effect of another



Susceptibility Gene/Locus

- A mutation that confers risk of disease.
- Often not the only cause of the disease.
- Will explain many cases but not all cases and will occur in unaffected individuals.



Odds ratio

- Geneticists way of determining that they have identified a risk locus.
- Odds ratio > 1 means that diseased animals are more likely to have the risk mutation than healthy animals.
- The ratio between two odds, the odds of individuals in the disease group having a specific allele, and the odds of individuals in the control group having the same allele.

Relative risk

- The risk of disease if the dog has the risk genotype.
- This is the important value for breeders.
- A relative risk of 2 means that dogs with the mutation are twice as likely to get the disease as dogs without the mutation.
- An odds ratio of 2 means that twice as many diseased dogs have the mutation as healthy dogs.

Molecular heterogeneity

- More than one gene can cause the same disease/trait.
- More than one change in a gene (mutation) can cause the same disease.

Some mutations are unidentified

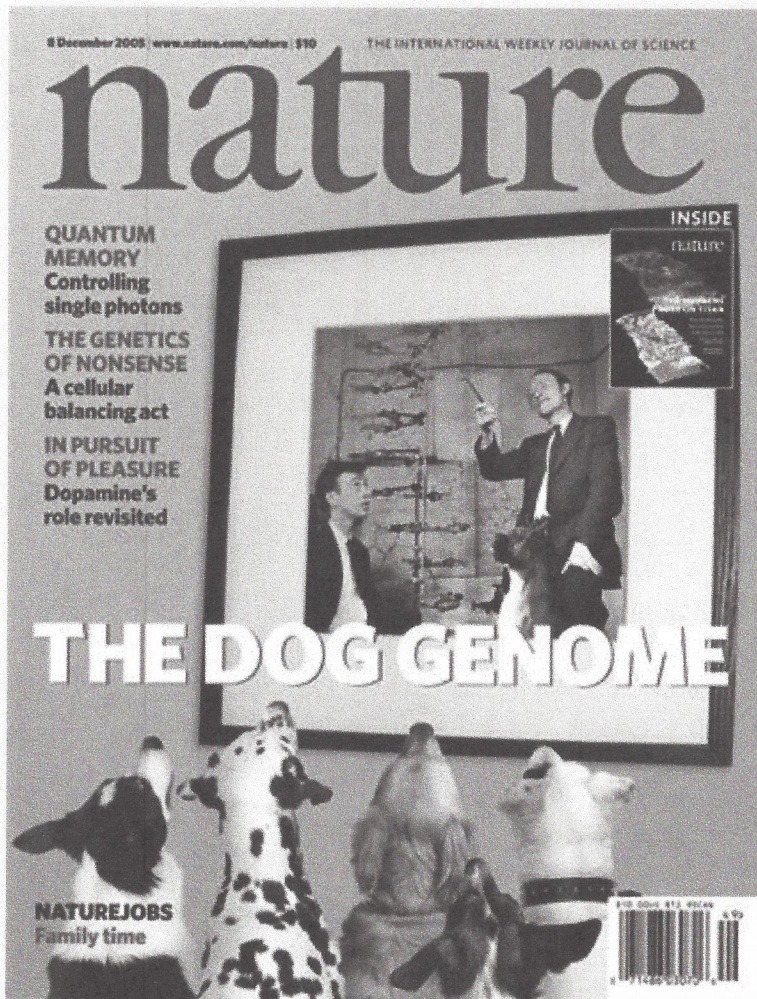
- Tests can be offered that test the chromosomal region rather than the exact mutation.
- These are called haplotype or indirect tests.
- They provide useful breeding information while research is ongoing.

G/G	A/G	G/G	G/G	G/G	G/G	A/G	G/G	G/G	G/G	G/G	G/G	G/G	G/G	A/G	G/G	G/G	A/G	A/G	G/G	G/G	G/G	G/G	G/G	A/G	G/G	A/G	G/G	G/G	G/G
G/G	A/G	G/G	G/G	G/G	G/G	A/G	G/G	G/G	G/G	G/G	G/G	G/G	G/G	A/G	G/G	G/G	A/G	A/G	G/G	G/G	G/G	G/G	G/G	A/G	G/G	A/G	G/G	G/G	G/G
G/G	A/G	G/G	G/G	G/G	G/G	A/G	G/G	G/G	G/G	G/G	G/G	G/G	G/G	A/G	G/G	G/G	A/G	A/G	G/G	G/G	G/G	G/G	G/G	A/G	G/G	A/G	G/G	G/G	G/G
A/A	A/C	A/A	A/A	A/A	A/A	A/C	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/C	A/A	A/A	A/C	A/C	A/A	A/A	A/A	A/A	A/A	A/C	A/A	A/C	A/A	A/A	A/A
G/G	A/G	G/G	G/G	G/G	G/G	A/G	G/G	G/G	G/G	G/G	G/G	G/G	G/G	A/G	G/G	G/G	A/G	A/G	G/G	G/G	G/G	G/G	G/G	A/G	G/G	A/G	G/G	G/G	G/G

Frequency of the mutation

- Allele frequency is the frequency of the mutation within the breed.
- It changes with testing and selection.
- Common or rare in a breed.
- Does it even exist within your breed.

Genome sequence

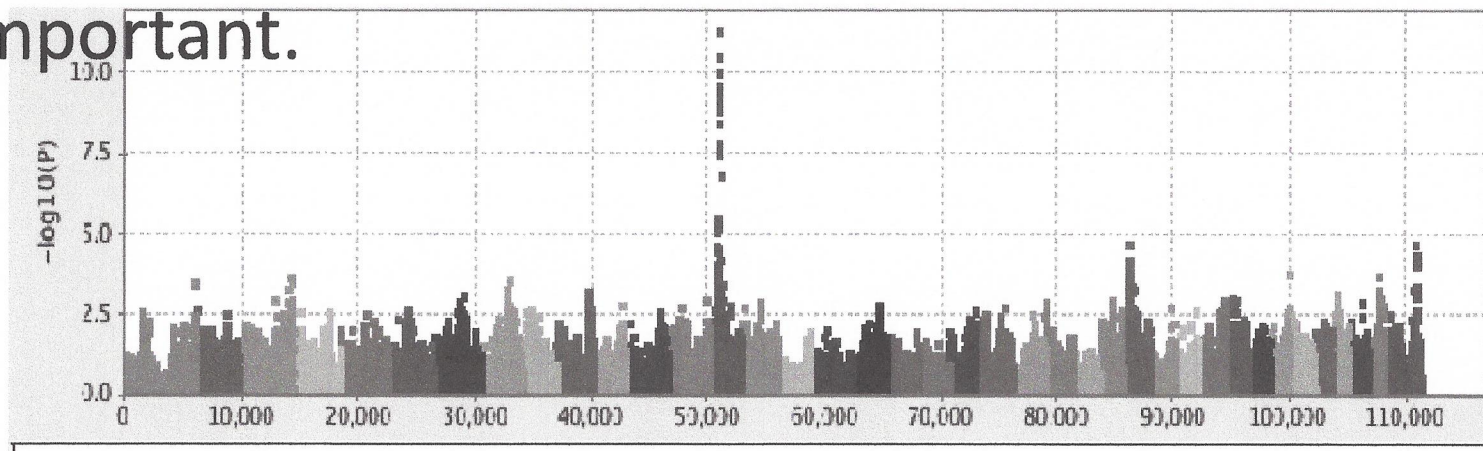


- Dog genome sequenced in 2005.
- Whole genome SNP genotyping arrays were developed for dogs.
 - Dog Affymetrix 50K
 - Dog Illumina canine HD 172K
- Genome sequence cost has decreased to ~ \$2,000/dog.

Genome Wide Association Study

GWAS

- Allows mapping of traits without collecting families, without knowing the mode of inheritance and with molecular heterogeneity.
- Low whole genome sequence costs allow fast detection of mutations.
- Verification in families and populations is still important.



Genetic tests

- The first disease causing mutation in dogs was found in 1989. It was a single nucleotide point mutation that caused an amino acid change in Factor IX leading to hemophilia B in a mixed breed dog (Evans *et al.* 1989).
- Presently there are over 300 disease causing mutations identified in dogs.

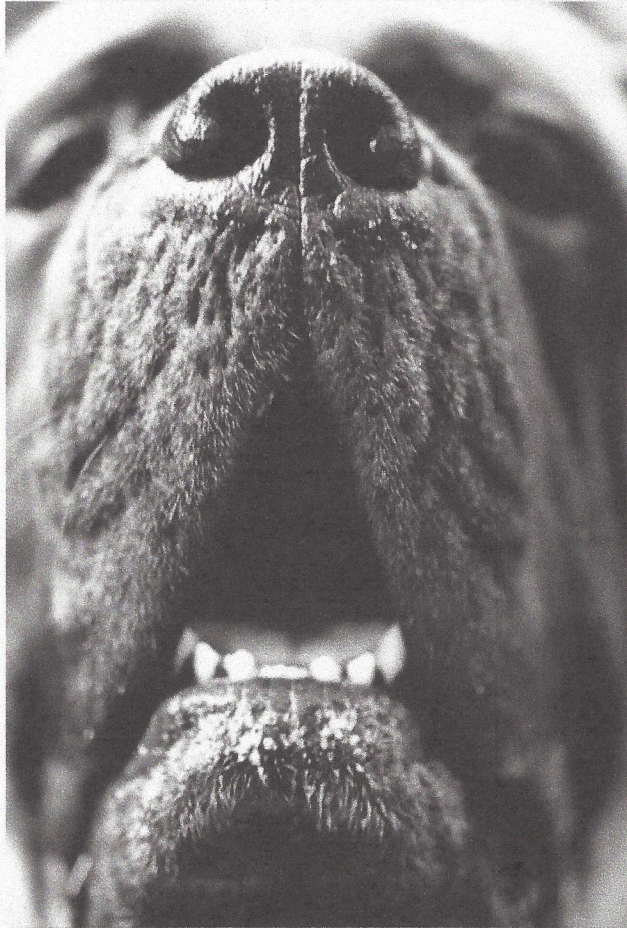
DNA tests

- Breed-specific
- Only test for the specific mutation that has been identified, NOT all possible mutations that could cause a similar disease.

Testing Labs

- The actual type of PCR assay that a company uses is usually proprietary.
- Quality control varies from company to company.
- DNA-based testing for animals is not regulated

1. No dog is genetically perfect.



- It will be difficult to identify a dog that does not carry any diseases and looks and acts close to the ideal of the breed.

2. Not every dog must be bred

No dog should be bred excessively!

3. Is the disease in your breed?



- Tests are offered to anyone who wants to pay for them.



4. What is the allele frequency?

- Is the disease common or rare

5. Is the disease treatable?

- A disease that is easily treatable may be one that you don't select against as strongly.

6. How severe is the disease?

- Does it cause pain and suffering?
- Separate from is it treatable
- Orthopedic diseases fit into this category.

7. What is the age of onset?

- Consider a disease that affects 12 year old dogs VS a disease that affects 1 year old dogs VS a disease that affects newborns.

8. What is the mode of inheritance?

- This **MUST** be known or there is no point in running the test



9. What is the penetrance of the disease?

- The mutation test for degenerative myelopathy (DM) has reduced penetrance.
- Sometimes this is a difficult number to obtain.
- If you found out that the number of dogs who will get a disease if they have a mutation is only 10% would you still run the test?

10. Is the test a marker test or a mutation test?

- Marker test should have error rates to indicate how good or bad they are.
- It should also be clear which type of test is being offered.

11. Is the test published?

- Publication in a peer-reviewed scientific journal means that the **science** has been evaluated by an independent group of scientists.
- It does not mean that they recommend testing, or that each lab that performs the test has the same QC as in the paper.
- Most of the time, ultimate proof that a mutation is causative of the disease is NOT available.

Tests available

- CHF has a list of tests available in dogs.
- Parent clubs should also have information about testing within the breed.
- Orthopedic foundation for animals



Questions?



Canine Projects ---- Bannasch Lab

Cleft palate/Lip - all breeds

Zena Wolf (ztwolf@ucdavis.edu)

Hypertrophic osteodystrophy - all breeds

Noa Safran DVM PhD
(dr.noa.safran@gmail.com)

Addison's disease - Nova Scotia Duck T. R .

Emily Brown
(eabrown@ucdavis.edu)

Glioma (Brain Tumor) ---- all breeds

Miriam Aguilar

Ectopic Ureters---- all breeds

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Neuroaxonal dystrophy --- Rottweiler

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NIDCR

NIAID

