Consequences of Selection

What's Love Got to do With It? The Many Things to Think About When Selecting Animals for Breeding

Dr Bert Klei PhD

Gibsonia PA

Introduction

WAGENINGEN UR
For quality of life

UNIVERSITY OF PITTSBURGH

UPMC

University of Pittsburgh
Medical Center

Main Message

What You See = Genes + Outside Influences

Phenotype = Genotype + Environment

$$P = G + E$$

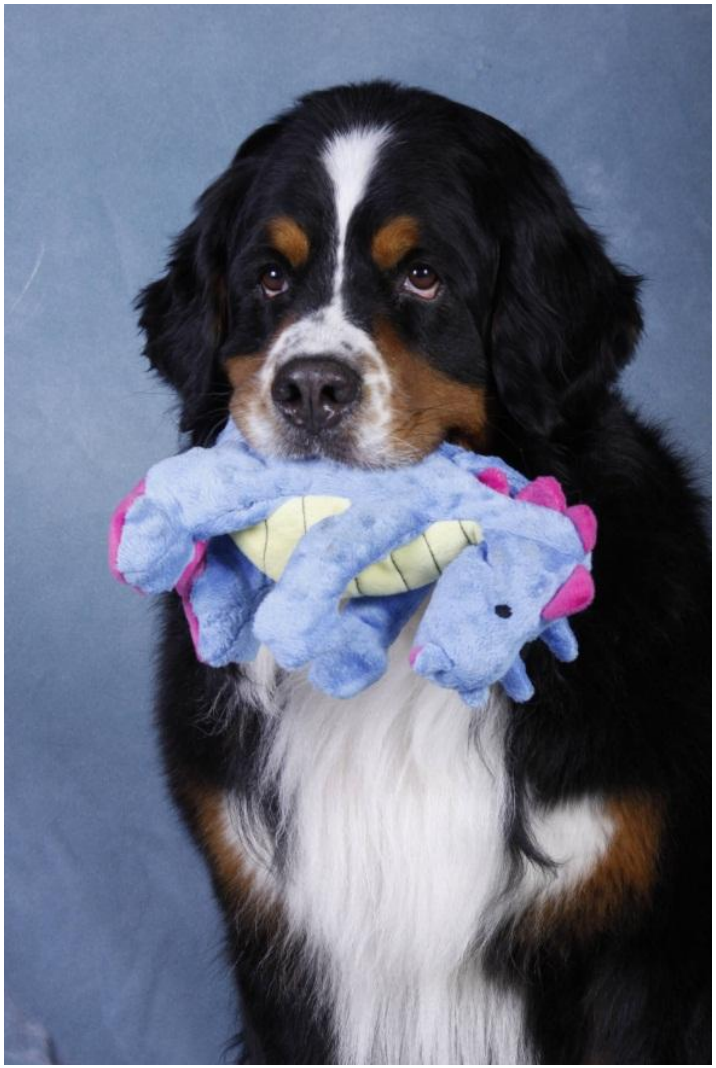
The Breeders Formula

Focus today is on G and how we can influence G to influence P

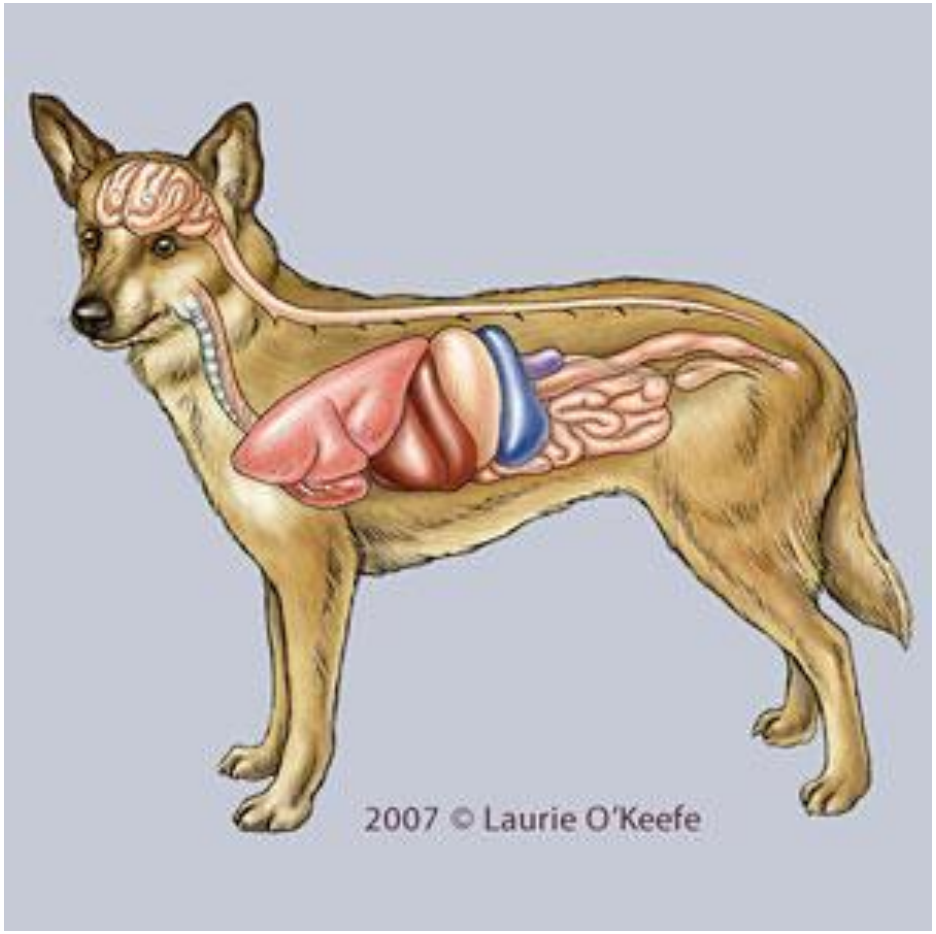
Today's Talk

- Basic Genetics
- How we can use basic genetics to better understand the various traits we are interested in.
- Strategies to make genetics work in your breeding program.

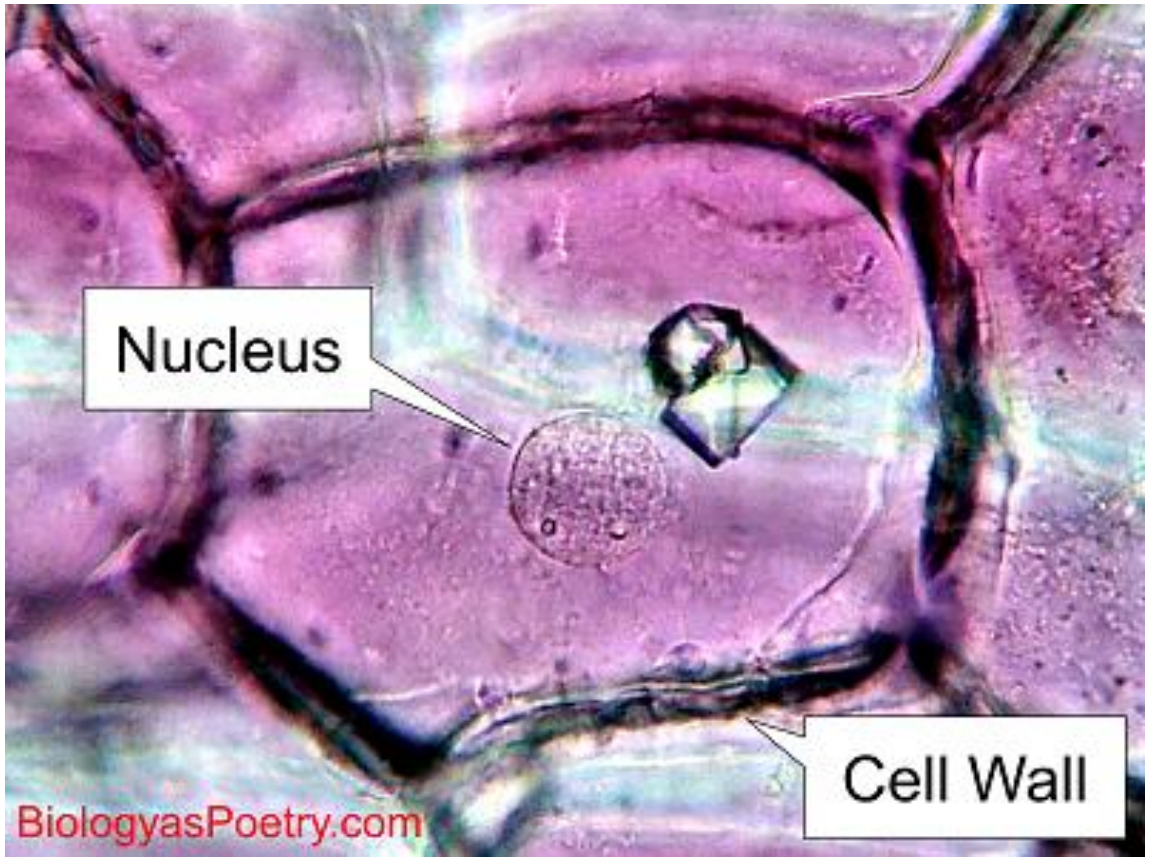
Journey to find my Genotype



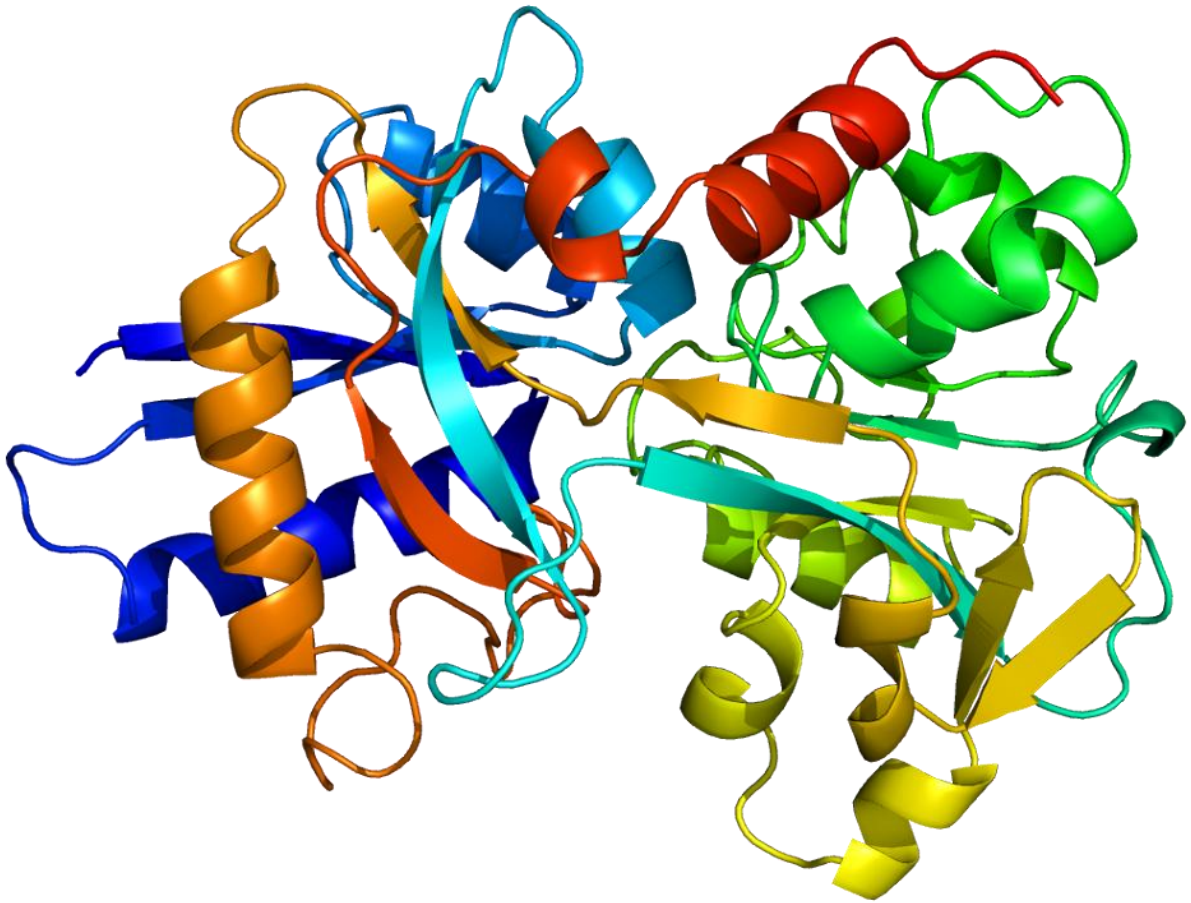
Organs



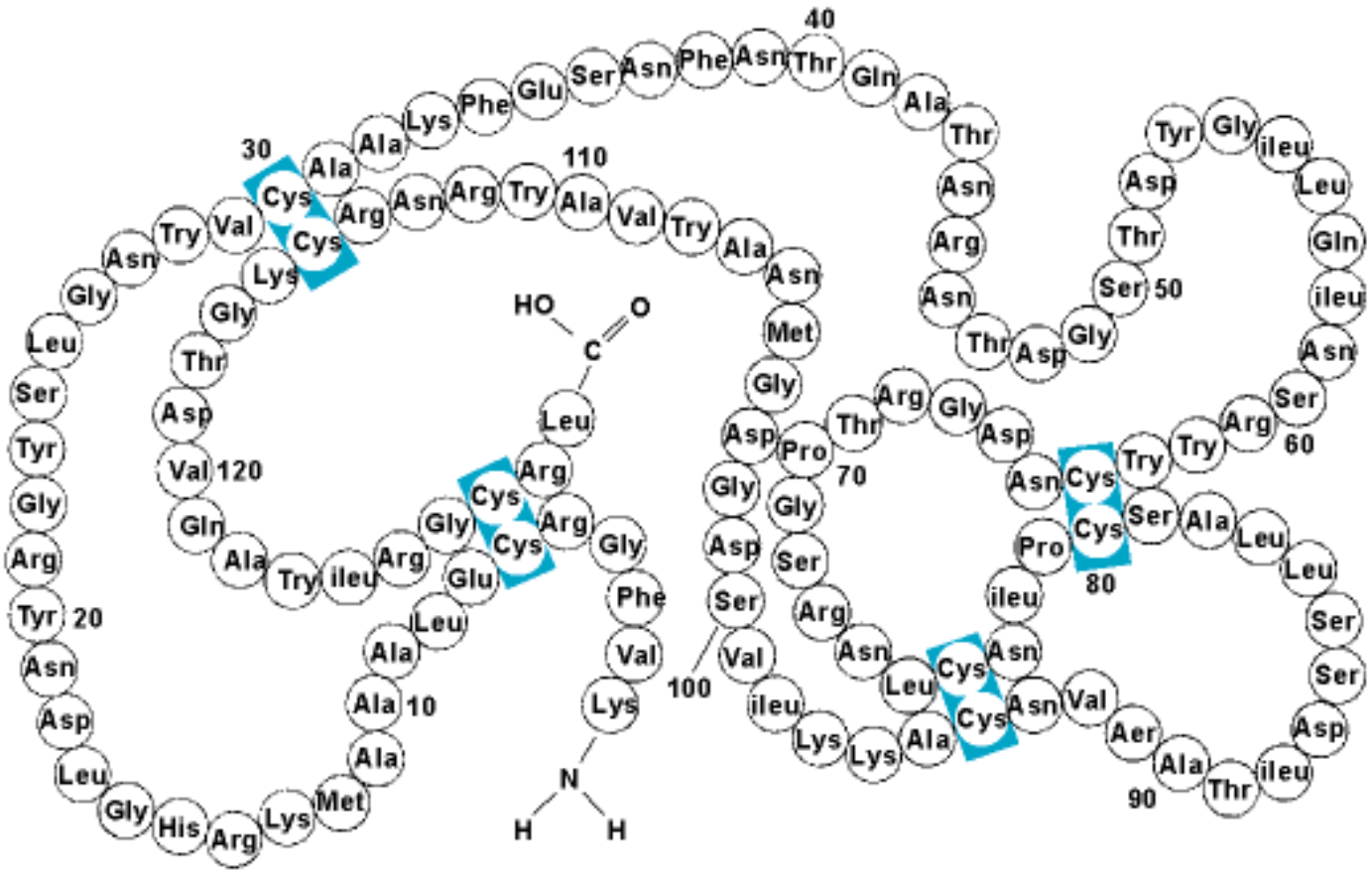
Cells



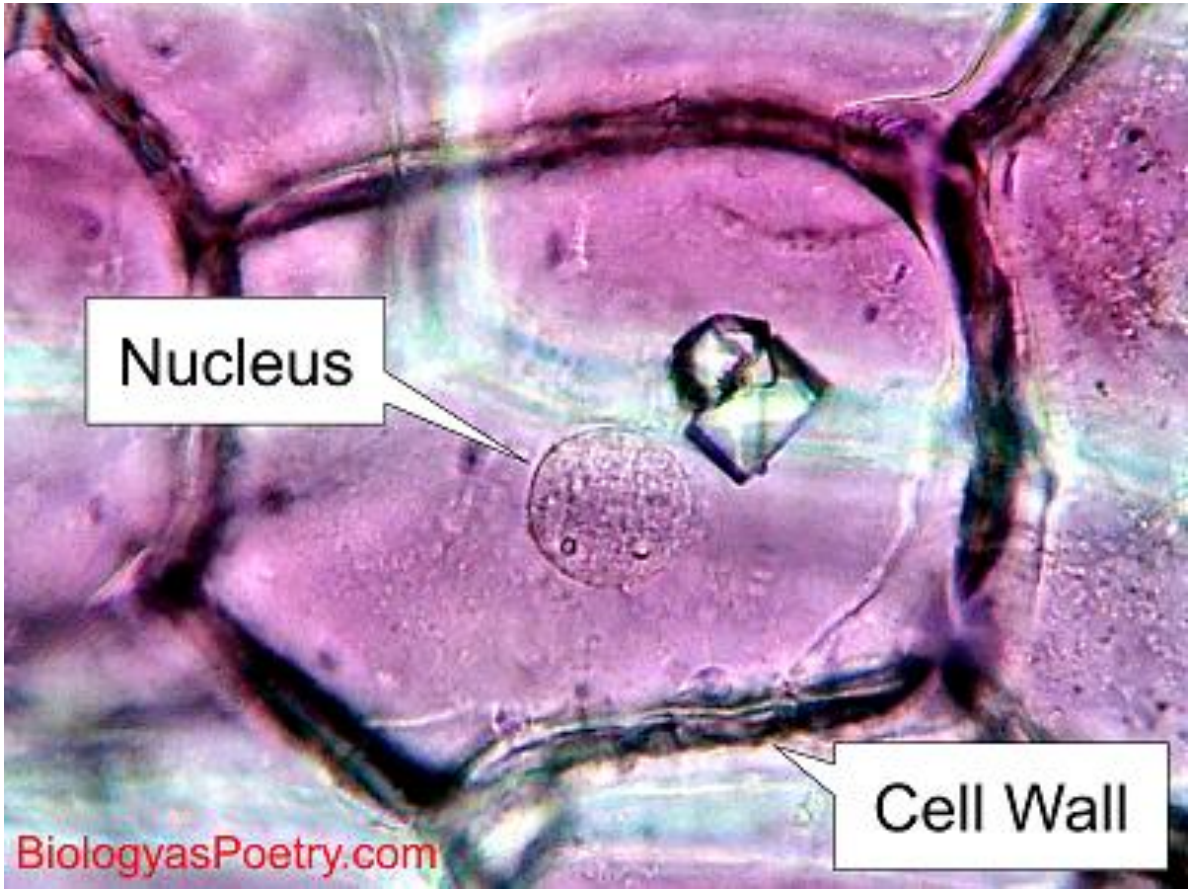
Proteins



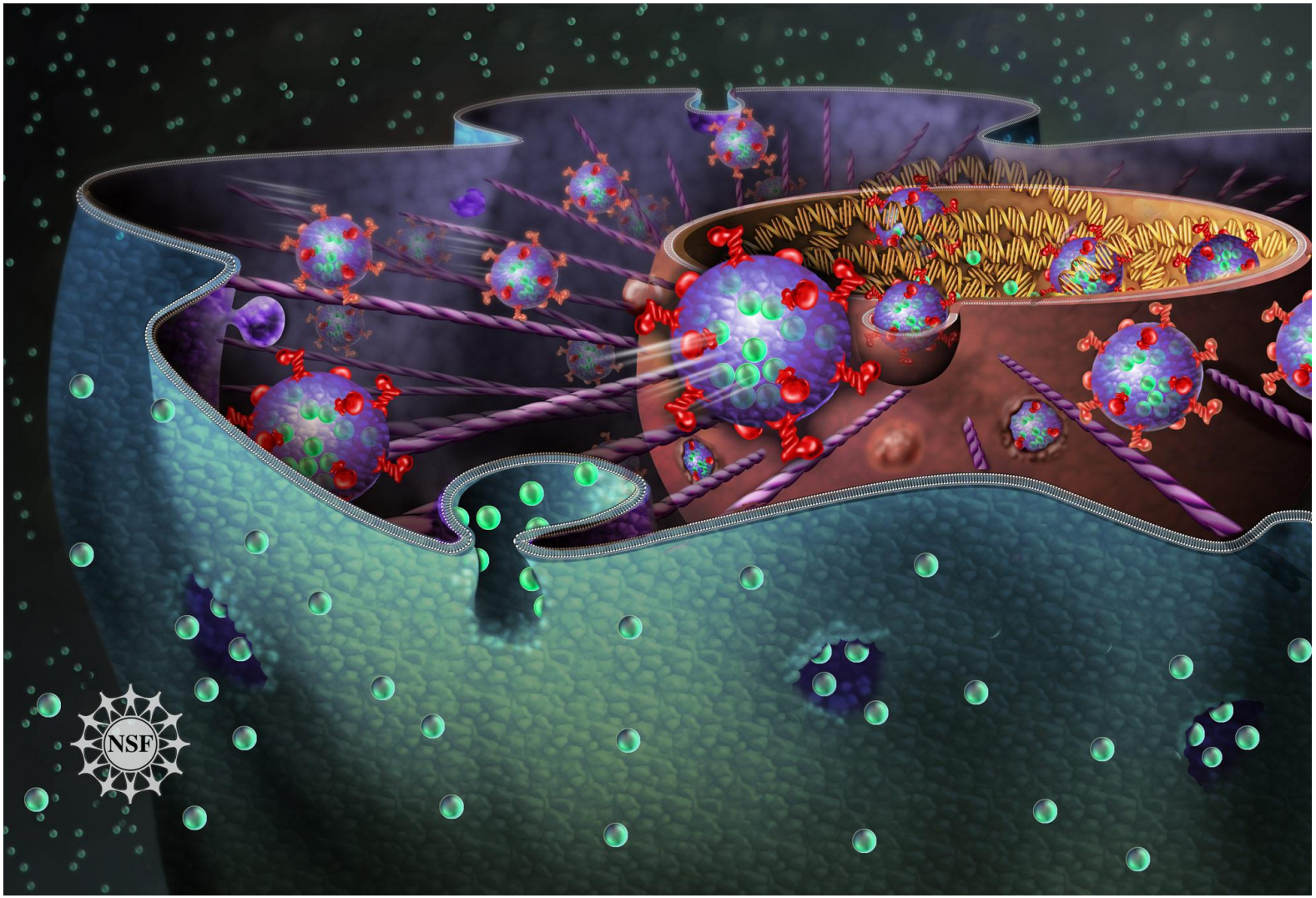
Amino Acids



Where does Genotype come in?



Nucleus

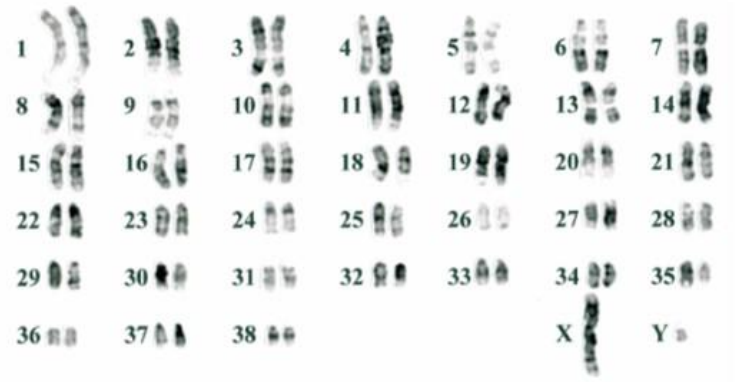


Chromosomes

Breen lab

Facts About Chromosomes

- Dog nucleus contains 78 chromosomes
- Organized in 39 pairs
- 1 in each pair from the sire
- 1 in each pair from the dam



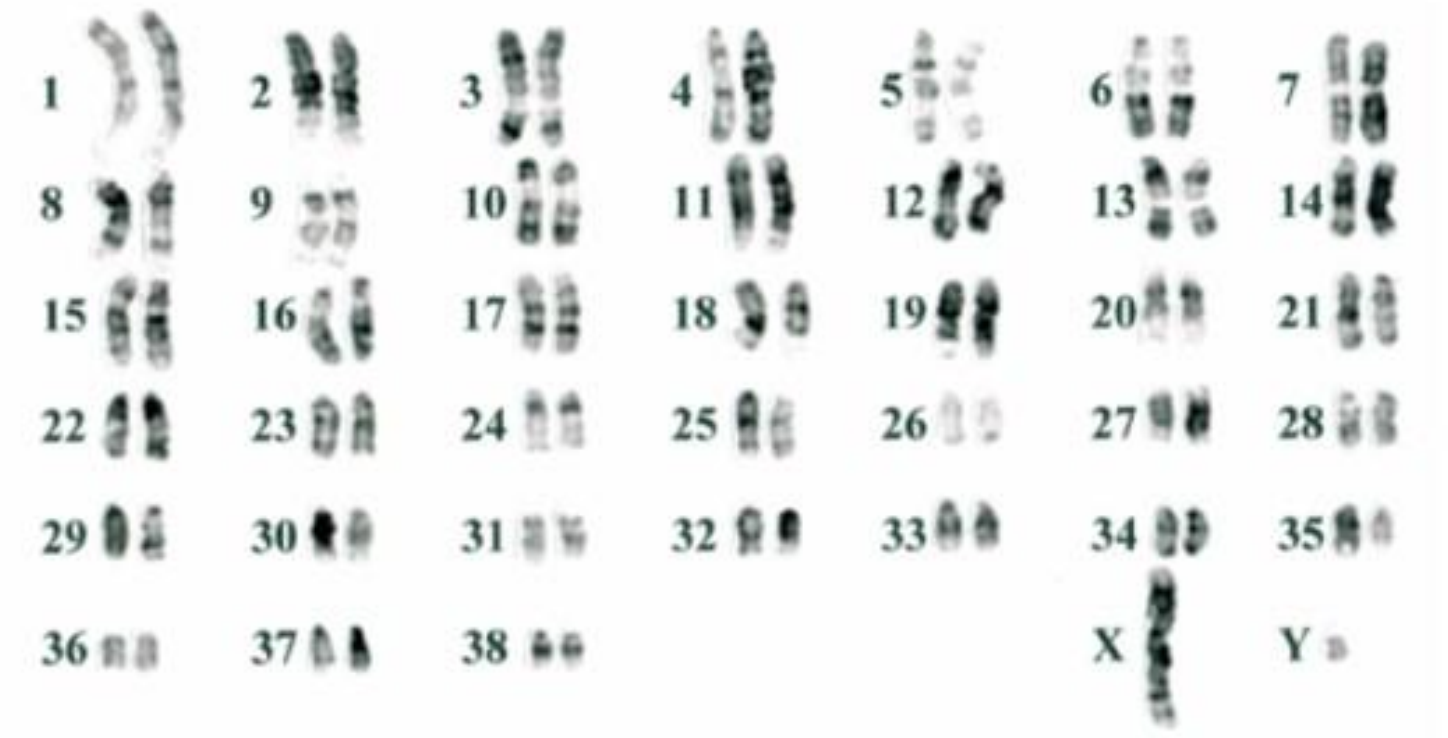
- During ***meiosis*** when the ***gametes*** (sperm and egg cells) are formed each pair is split at random.
- Total number of possible combinations is:
  - 2^{39} = 549,755,813,888 = 0.5 trillion.

Breeder's Challenge

- How to control this random process to breed a better dog?

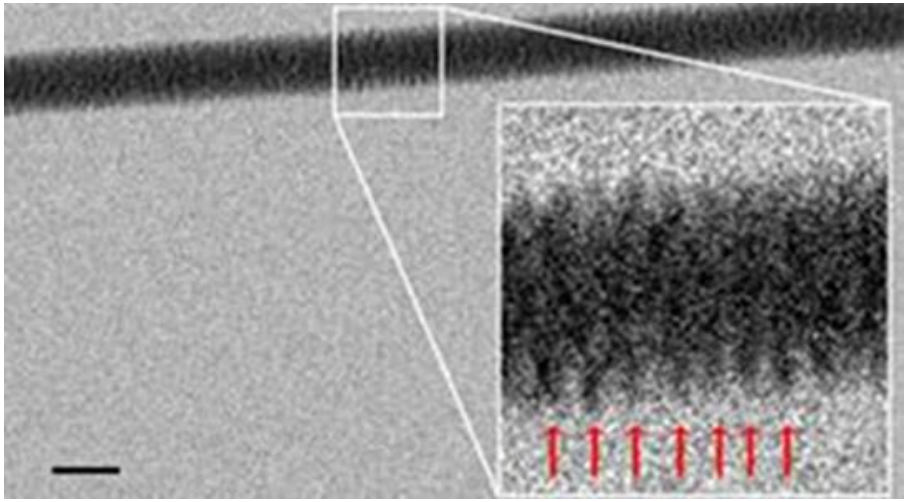
- Question: Half the chromosomes come from the sire and half come from the dam. This is always the case. What fraction comes from each of the grandparents?
- Answer: On average 25%.
- It can range from 0% to 50%
- With heavy inbreeding one could be contributing all the chromosomes.

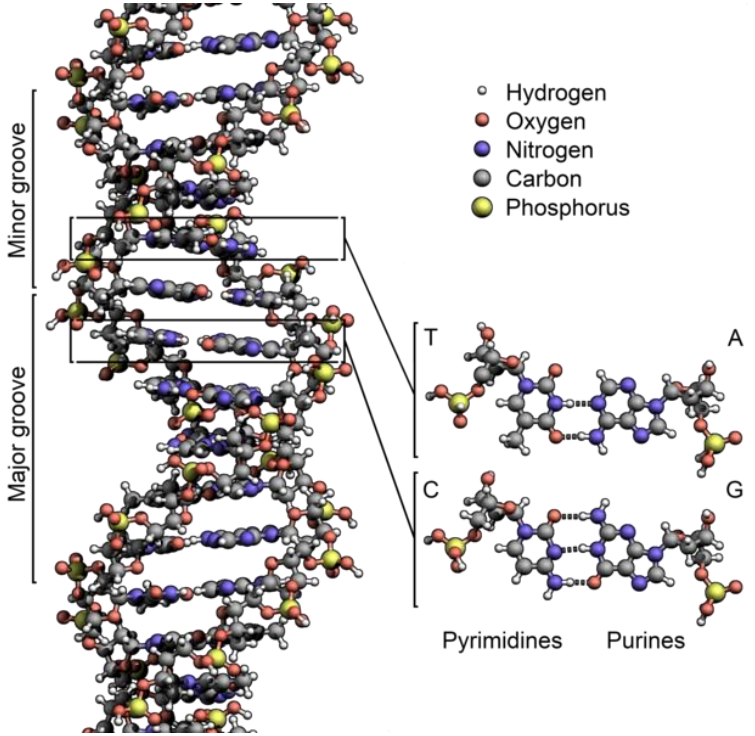
Chromsomes



Breen lab

DNA

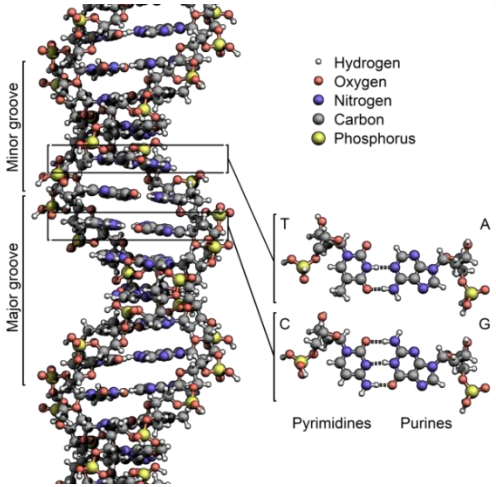




DeoxyriboNucleic Acid

Nucleotides

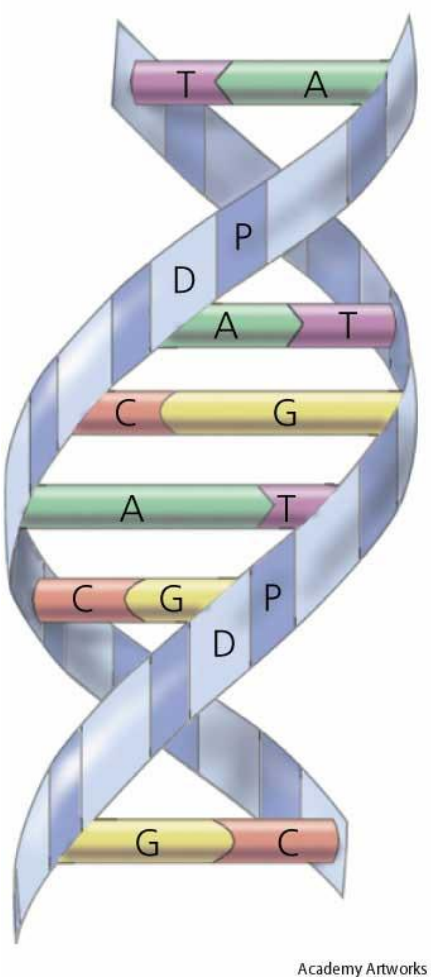
- There are four nucleotides:
  - Adenine (A)
  - Cytosine (C)
  - Guanine (G)
  - Thymine (T)



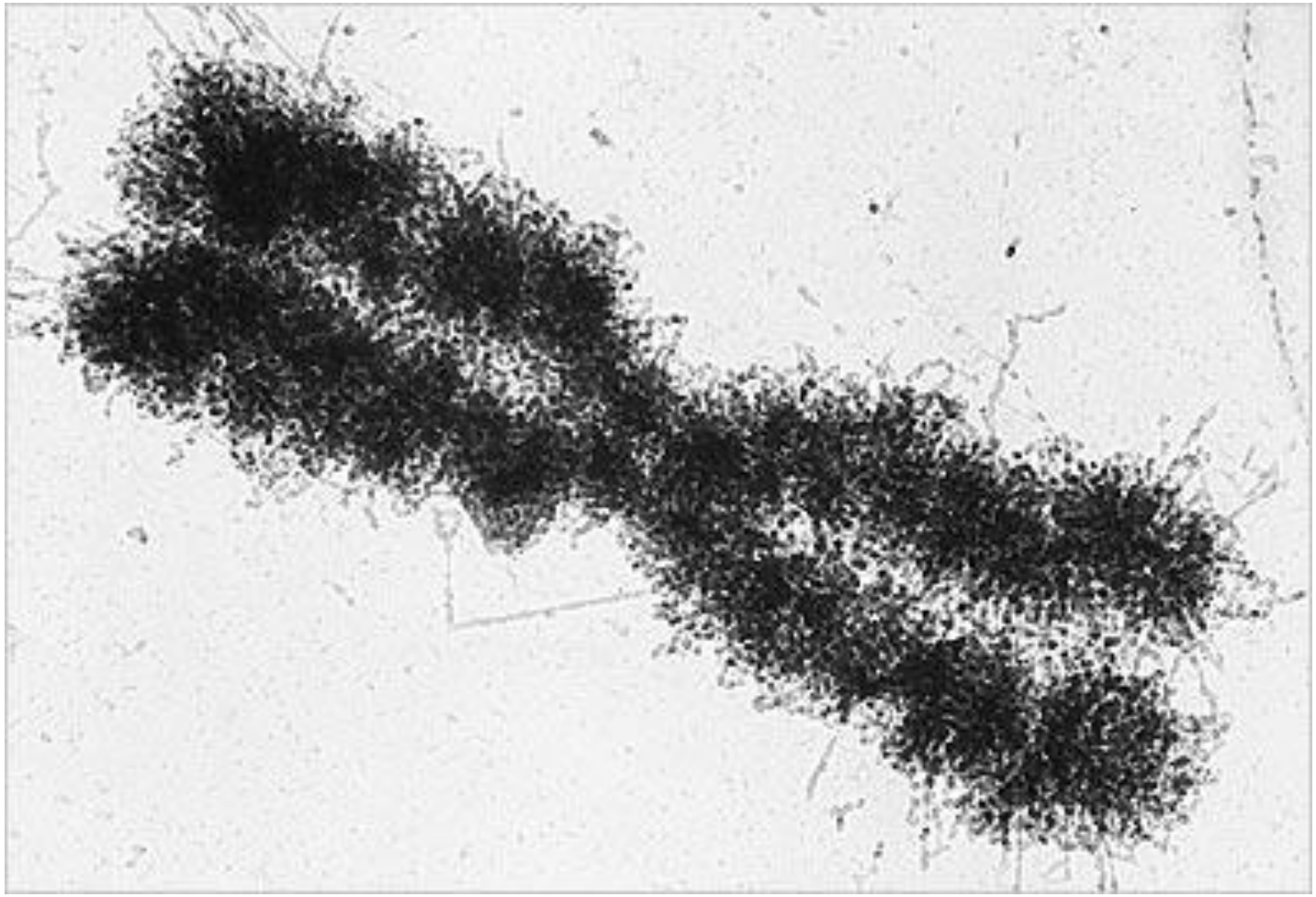
- These are all that is needed to encode the genetic code to build a dog.

Facts about DNA

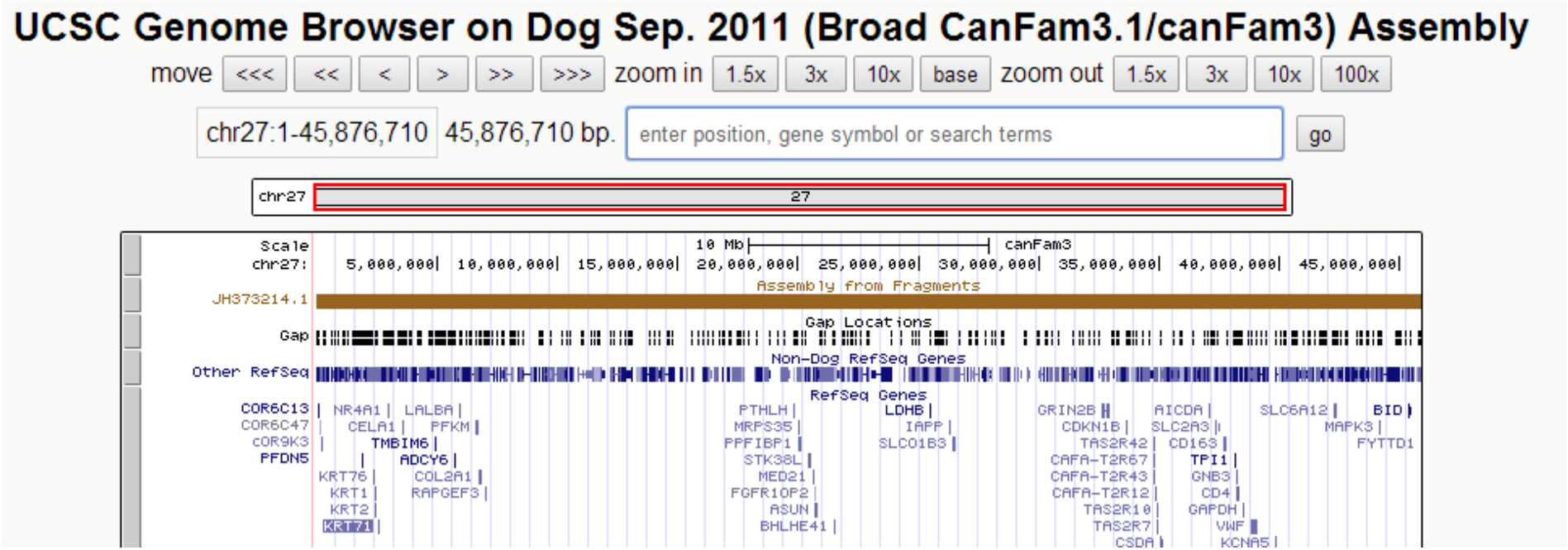
- DNA is build up out of two strands
- When A on one strand, always a T on the other, same with C and G.
- One set of matched nucleotides is called a base pair.
- There are ~ 3,000,000,000 billion base pairs in the dog genome.



Chromosome

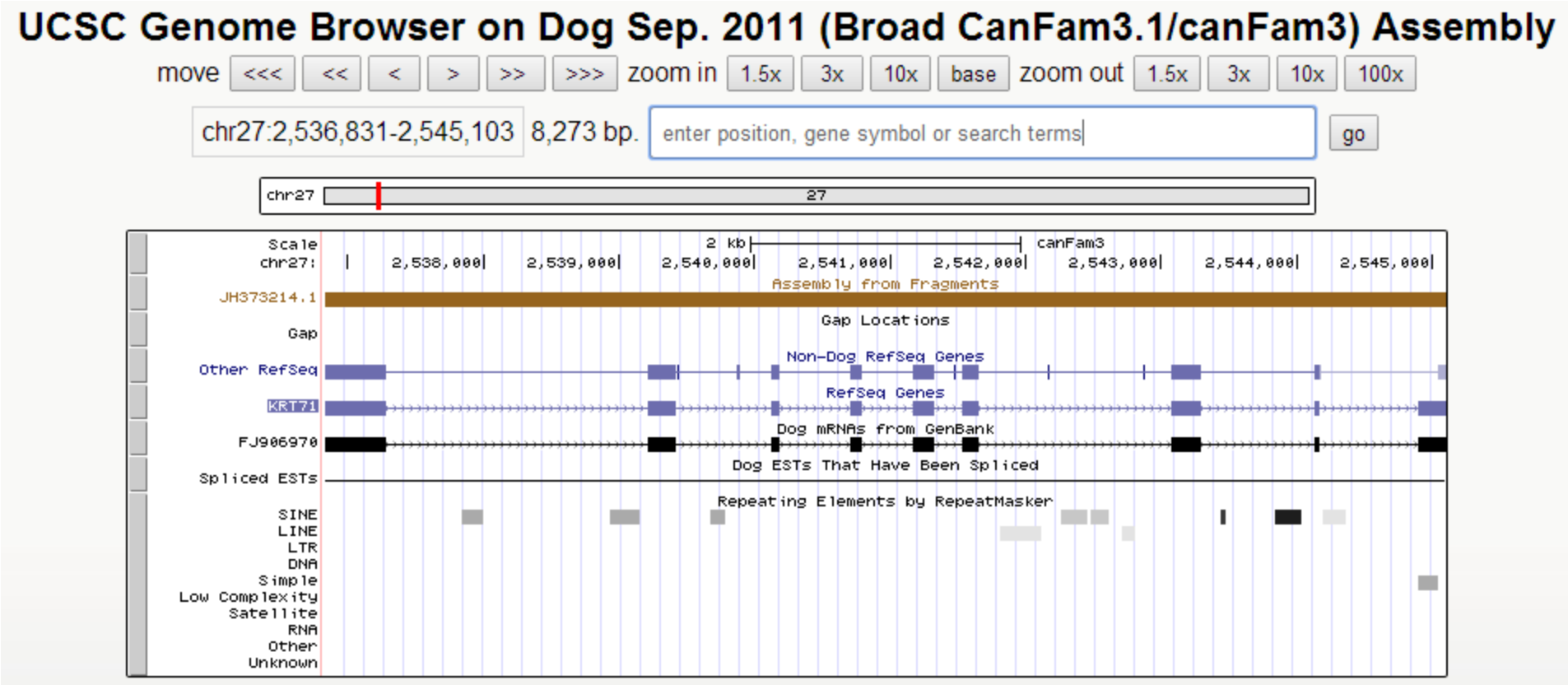


Genes



- Notice that there are large gaps between genes

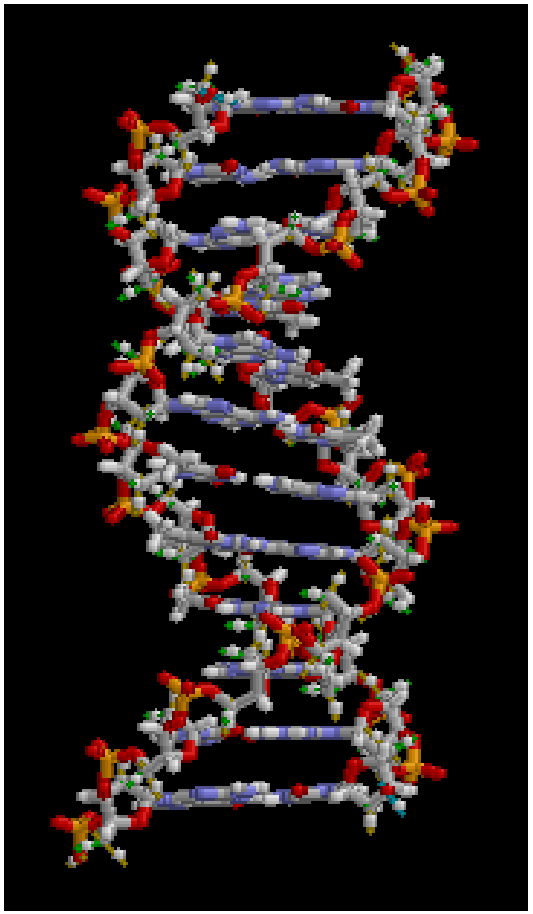
KRT71



- Notice the blocks and lines
- Blocks are called ***exons***, these are coding regions
- Lines are called ***introns***, these are non-coding regions

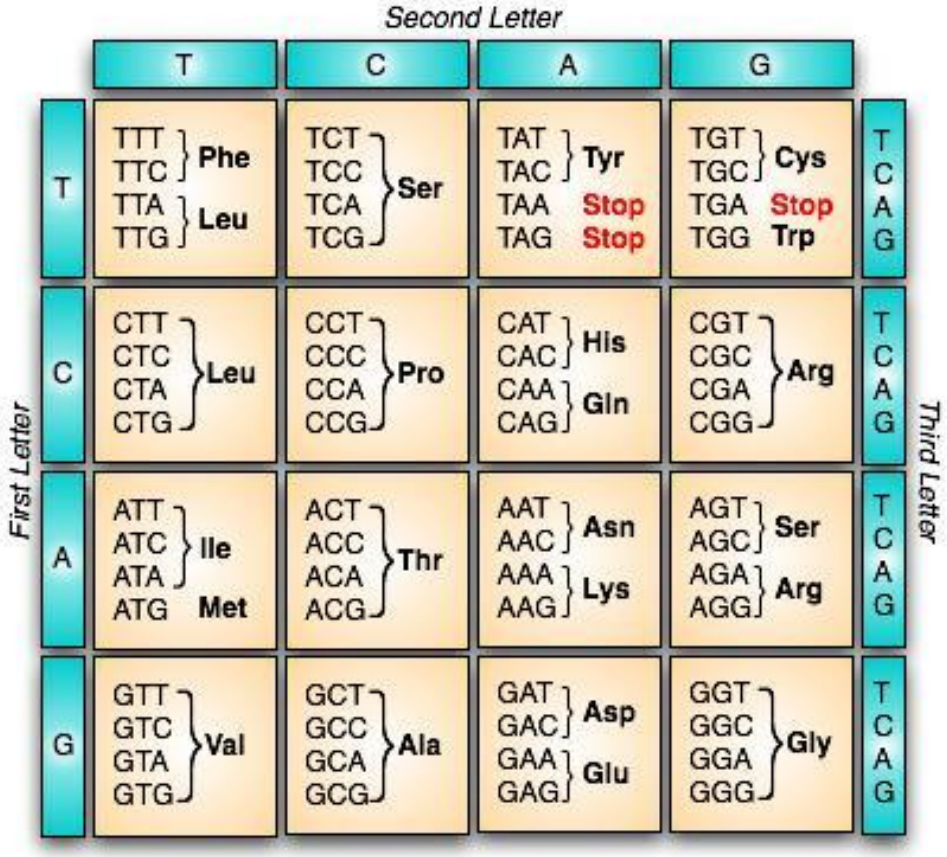
More Facts

- 98% is believed to be “non-coding”
- 2% is believed to contain the genetic code and is organized in ***genes***.
- The non-coding regions do contain things like promoters and enhancers and is not believed to be just “junk”.

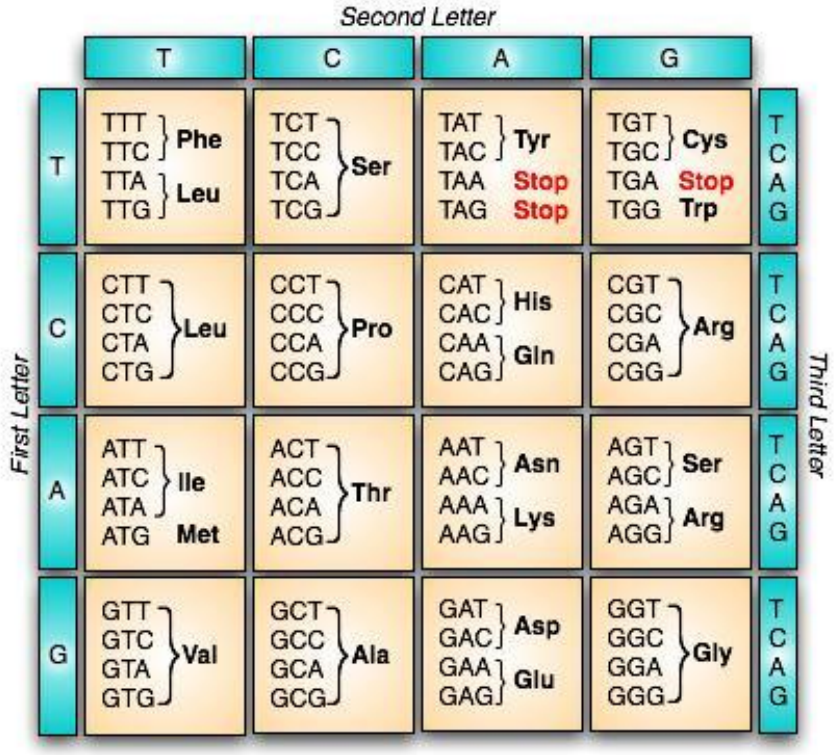


Exons

- In exons, 3 nucleotides in a row form words (***codons***).
- These codons are genetic code for amino-acids.

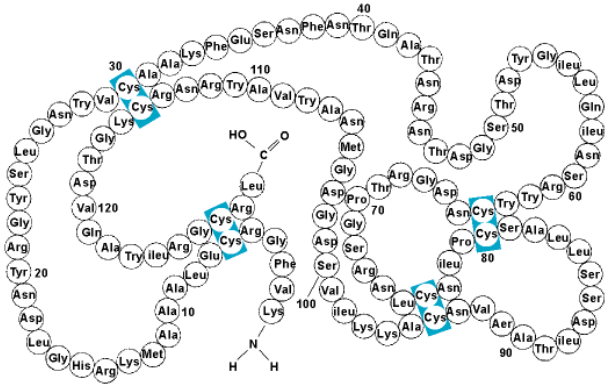


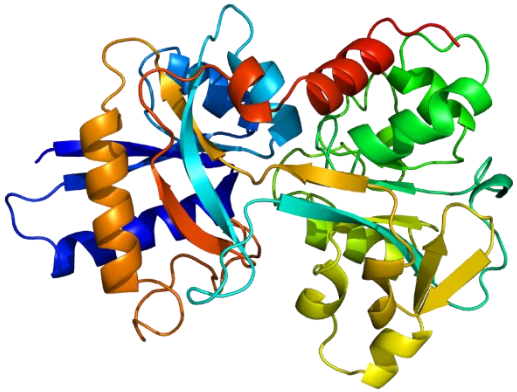
Proteins

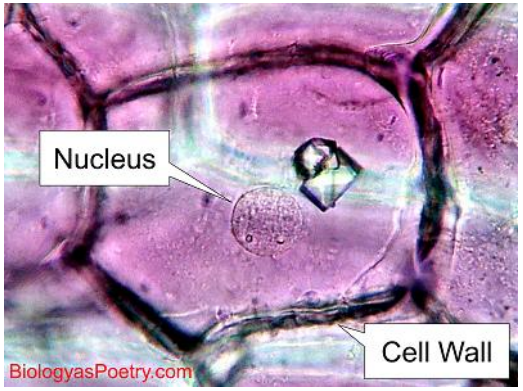


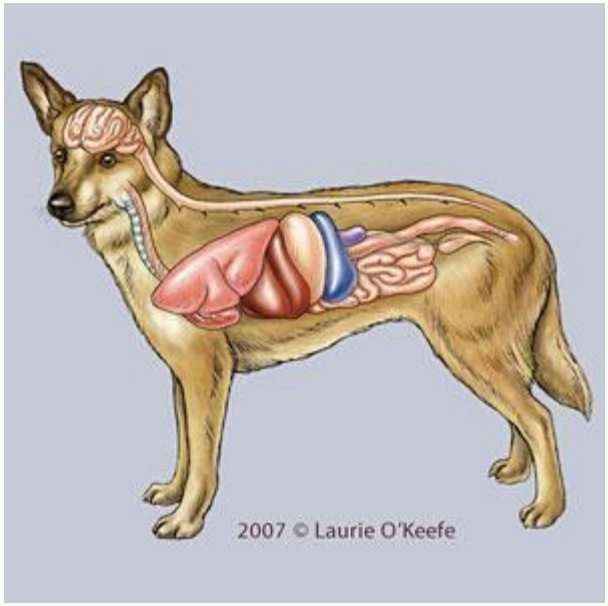
Codon	ATG	ACG	GAG	CTT	CGG	AGC	TAG
AA	Met	Thr	Glu	Leu	Arg	Ser	STOP

This how Genetics Shape your Dog



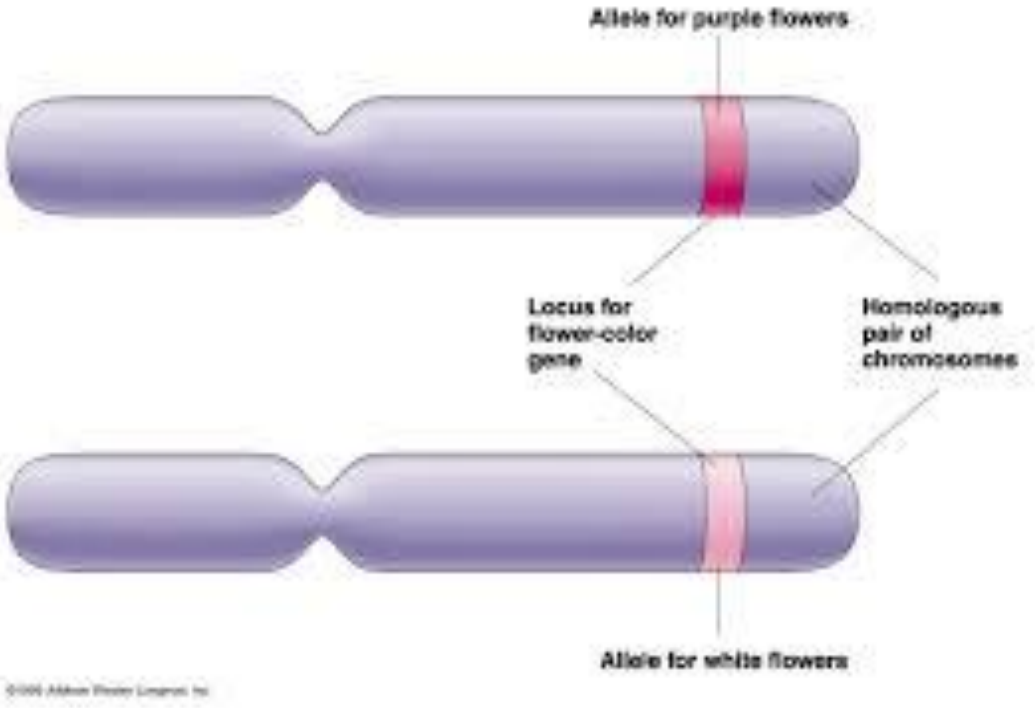






Let’s Talk Genetics

Locus and Alleles



- ***Locus*** is the position on the chromosome
- ***Allele*** is the variant of DNA

About Locus and Alleles

- Many people think of genes as loci and variant as alleles.
- The gene for coat color is a locus
- It has two alleles, one for a Black coat the other for a Red coat

About Locus and Alleles

- Modern genetics thinks of each base pair where there is a different nucleotide as a locus with different alleles.
- These are called SNP or single nucleotide polymorphisms
- In SOD1 the locus is *SOD1:c118* with alleles G and T

Example

Dog 1 - ACTGACCGTGAAAGGGCTTGATCGATTACATACGGCGCG

Dog 1 - ACTGACCGTGAAAGGGCTTGATCGATTACATACGGCGCG

Dog 2 - ACTGACCGTGAAAGGGCTTGATCGATTACATACGGCGCG

Dog 2 - ACTGACCGTGAAAGCGCTTGATCGATTACATACGGCGCG

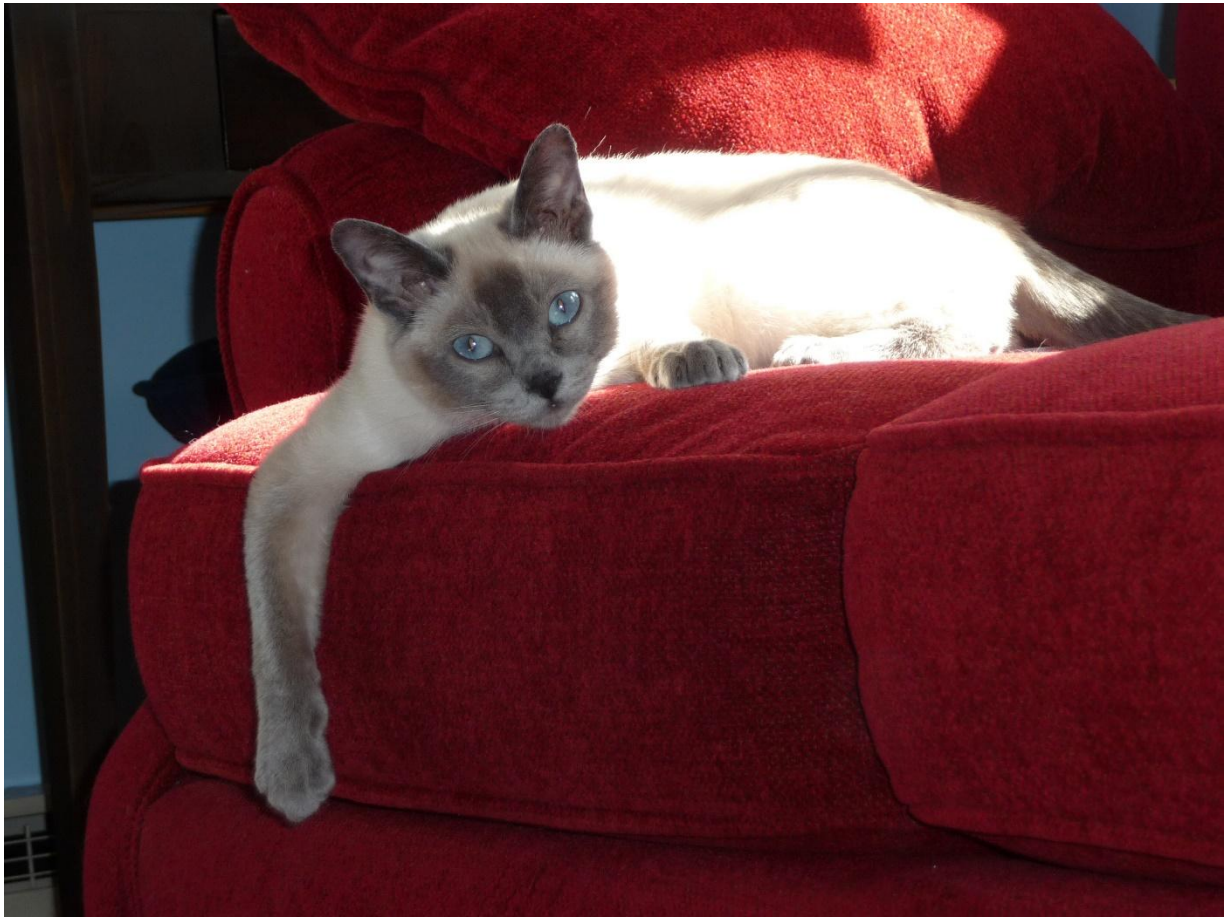
- Base pair 15 is a locus
- The locus has two alleles G and C.

Homozygous vs Heterozygous

- When the two alleles at a locus are the same we call this animal homozygous at the locus
- When the two alleles at a locus are different we call this animal heterozygous at this locus

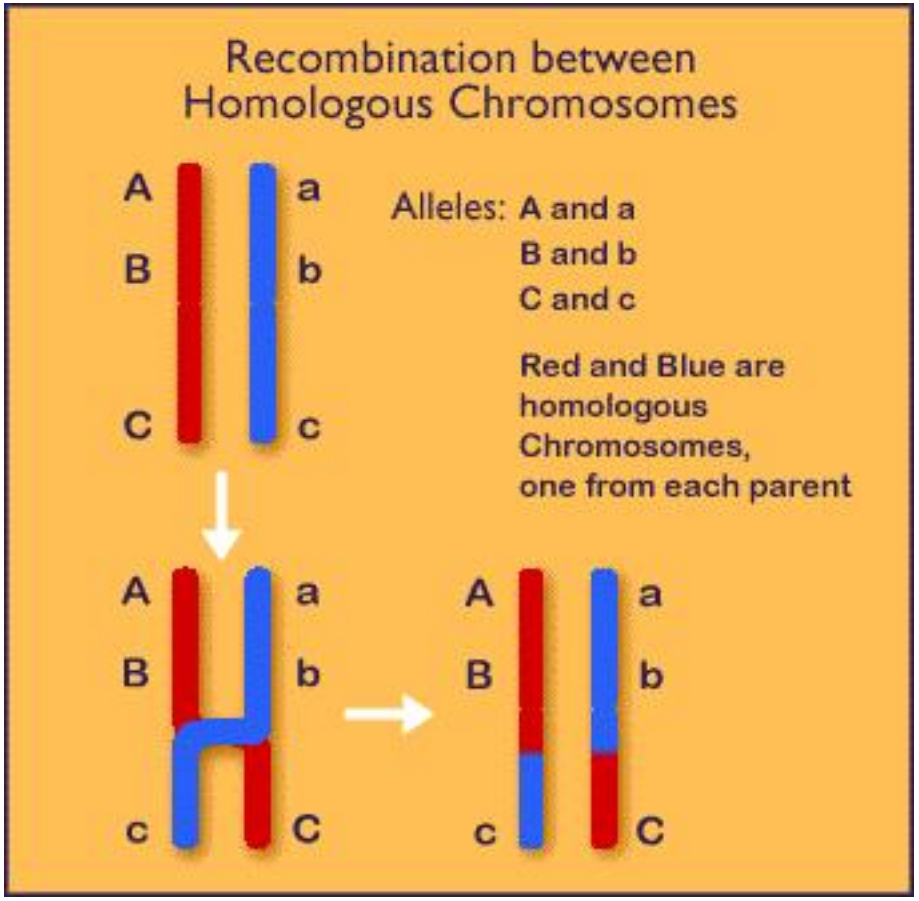
- Coat color
  - BB
  - RR
  - BR
- Degenerative Myelopathy
  - NA
  - AA
  - NN

Variation



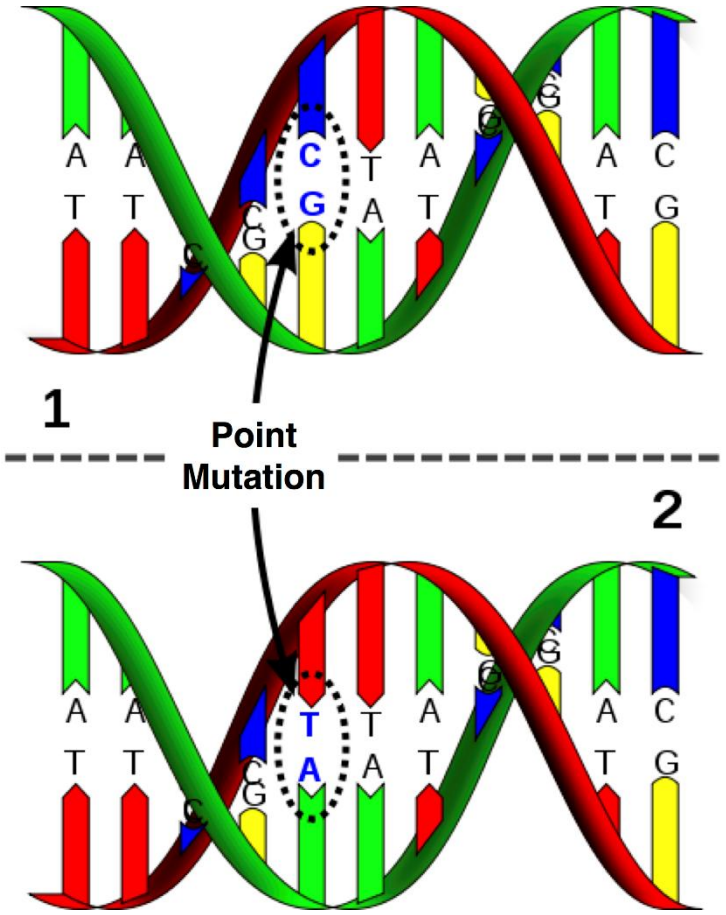
Recombination

- Process by which the two chromosomes of a pair exchange DNA



Mutation

- A mutation is a change in the nucleotide sequence.
- It occurs ~1:100,000,000 nucleotides
- Rate varies across the genome
- With 3,000,000,000 nucleotides in the genome, on average ~30 new mutations per individuals
- Rate varies across the genome
- Mutations are inherited



Silent Mutation

Codon	ATG	ACG	GAG	CTT	CGG	AGC	TAG
AA	Met	Thr	Glu	Leu	Arg	Ser	STOP

Codon	ATG	ACG	GAG	CTC	CGG	AGC	TAG
AA	Met	Thr	Glu	Leu	Arg	Ser	STOP

- The substitution of the T allele by a C allele at locus 12 does not affect the amino-acid it codes for.
- Very little harm done.

Missense Mutation

Codon	ATG	ACG	GAG	CTT	CGG	AGC	TAG
AA	Met	Thr	Glu	Leu	Arg	Ser	STOP

Codon	ATG	AAG	GAG	CTT	CGG	AGC	TAG
AA	Met	Lys	Glu	Leu	Arg	Ser	STOP

- The substitution of the C allele by a A allele at locus 5 does affect the amino-acid it codes for Thr → Lys
- Potentially damaging
- This is the type of mutation in *SOD1:c118*

Nonsense Mutation

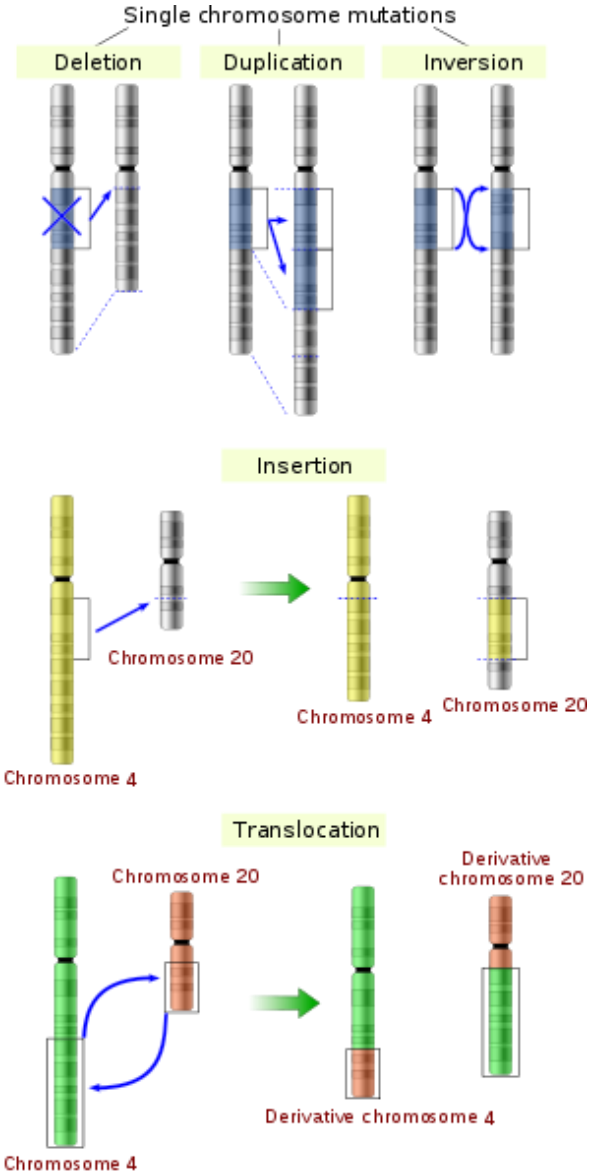
Codon	ATG	ACG	GAG	CTT	CGG	AGC	TAG
AA	Met	Thr	Glu	Leu	Arg	Ser	STOP

Codon	ATG	ACG	TAG	CTT	CGG	AGC	TAG
AA	Met	Thr	STOP	Leu	Arg	Ser	STOP

- The substitution of the G allele by a T allele at locus 5 does cause the transcription to STOP
- Probably damaging
- Cystinuria in Newfoundland Dogs is due to a nonsense mutation in SLC3A1

Another Nonsense Mutation

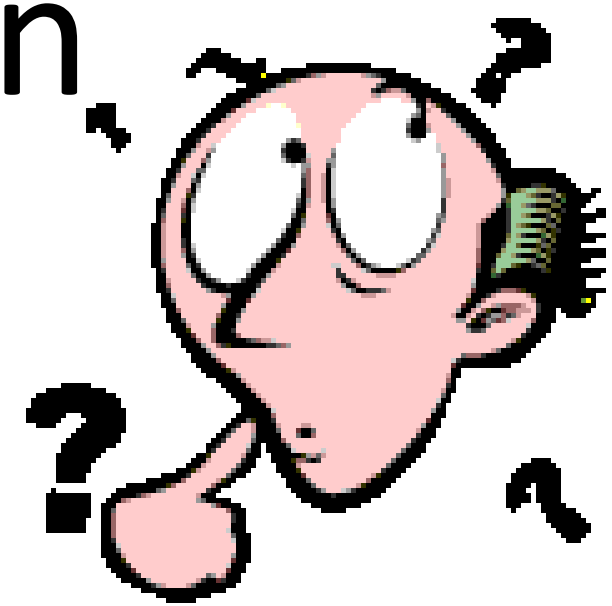
Other Kinds of Mutations



- Usually involves large pieces of DNA
- Changes the length of the chromosomes
- Very often seen in cancers
- Can cause major phenotypic differences.

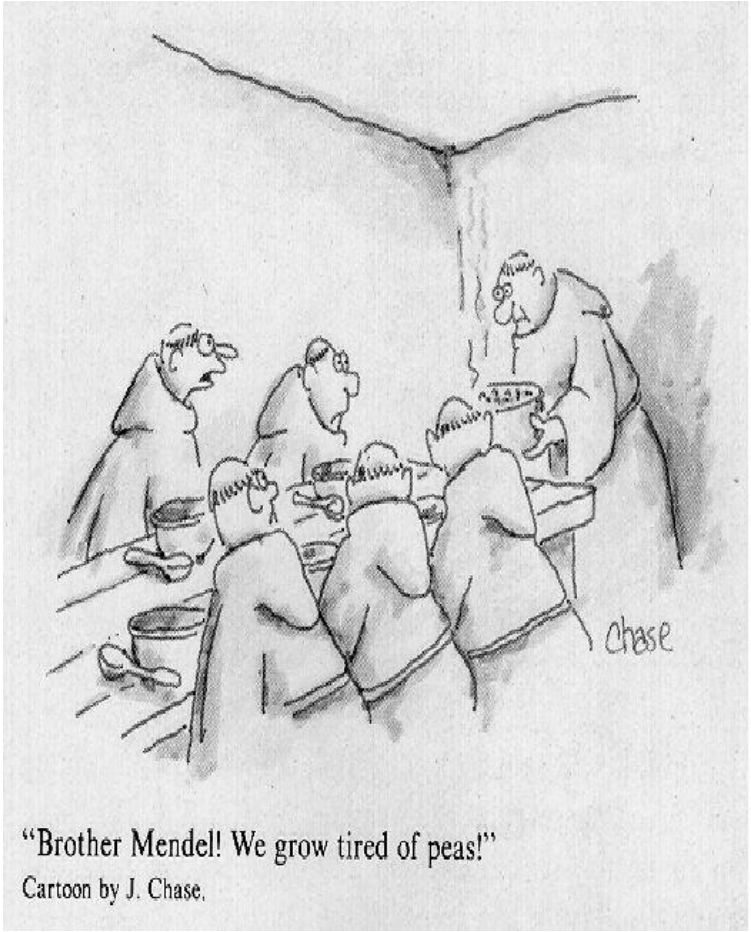
The Breeders Job

Manage Genetic Variation



Mode of Inheritance

- To manage and possibly control variation we need to understand how the variation is transmitted across generation.
- In other words we need to know the mode of inheritance.
- The mode of inheritance refers to one of the loci at an allele.



"Brother Mendel! We grow tired of peas!"
Cartoon by J. Chase.

Main Modes of Inheritance

- The mode of inheritance of an allele refers to whether the allele is expressed in the heterozygote
- Two alleles A and B
- Three possible genotypes AA, AB, and BB
- A is ***additive***
  - The phenotype of AB is midway between AA and AB
- A is ***dominant***
  - The phenotype of AB is the same as AA
- A is ***recessive***
  - The phenotype of AB is the same as BB

Made Up Example

- Black fur gene.
- A nonsense mutation caused the transcription of this gene to stop early.
- The black fur protein is not produced and a dog without the black fur allele has a red coat.
- One copy of the black gene is sufficient to have a black coat.
- There are two alleles B (black) and b (not black) at the black fur locus.

Example Continued

- BB – black fur
- Bb – black fur
- bb – red fur
- What is the mode of inheritance of the B allele?

  B is dominant

- What is the mode of inheritance of the b allele?

  b is recessive

Another Made Up Example

- One homozygote has curly hair
- Other homozygote has straight hair
- Heterozygote has wavy hair

- Curly = CC
- Straight = SS
- Wavy = SC or CS

- Co-dominant
- Additive

Continuous Traits

- Think of phenotypes influenced by many genes
  - Height, Weight, Penn Hip, Number of puppies in a litter

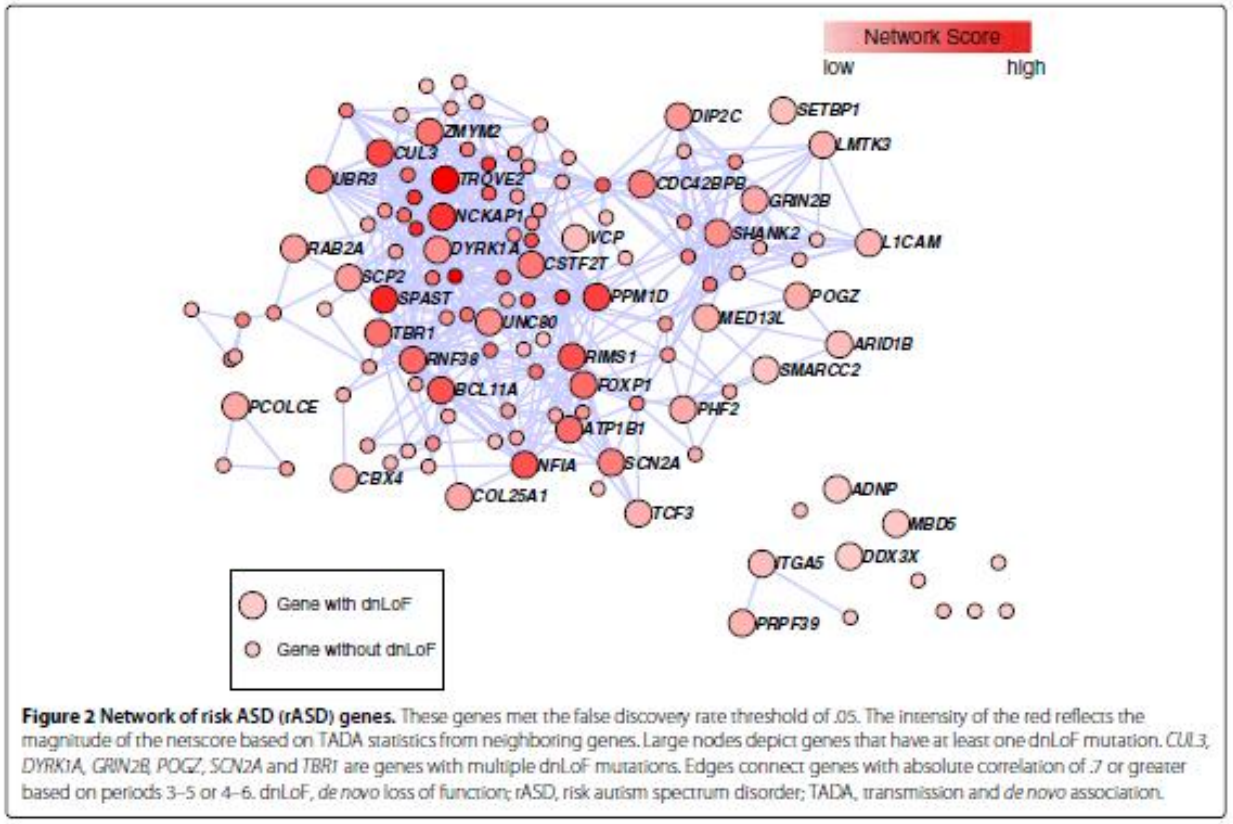
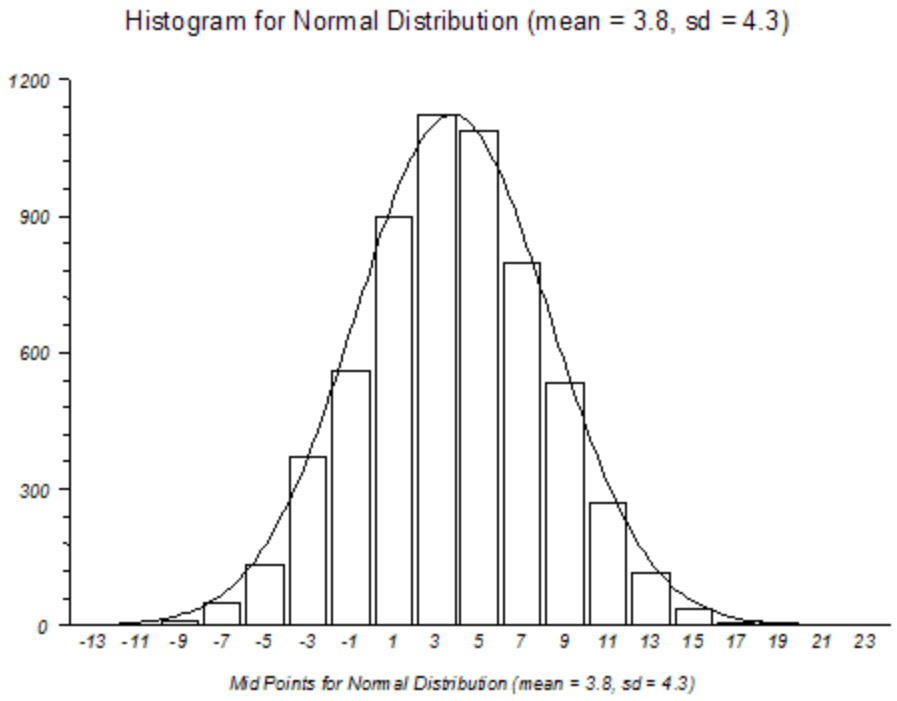


Figure 2 Network of risk ASD (rASD) genes. These genes met the false discovery rate threshold of .05. The intensity of the red reflects the magnitude of the netscore based on TADA statistics from neighboring genes. Large nodes depict genes that have at least one dnLoF mutation. *CUL3*, *DYRK1A*, *GRIN2B*, *POGZ*, *SCN2A* and *TBR1* are genes with multiple dnLoF mutations. Edges connect genes with absolute correlation of .7 or greater based on periods 3–5 or 4–6. dnLoF, *de novo* loss of function; rASD, risk autism spectrum disorder; TADA, transmission and *de novo* association.

Liu et al., 2014

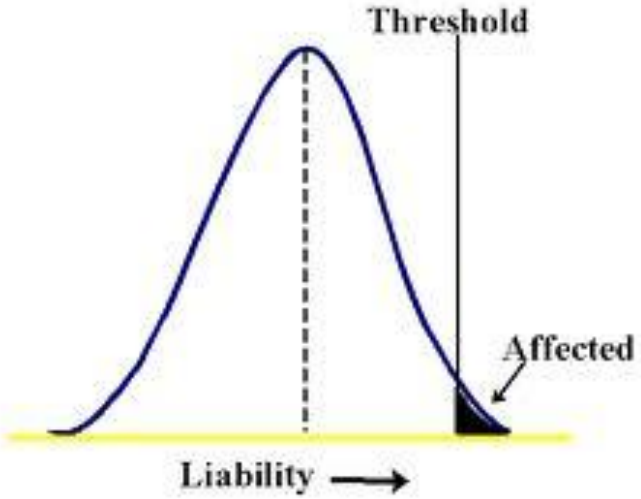
Bell Shaped Cuve

- Histogram of outcomes



Threshold Traits

- Outcomes are usually yes/no, 0/1, affected/unaffected
- Simple single gene model does not explain the outcome.



- There is an underlying continuous liability phenotype
- Once you go over a certain level of this phenotype you become affected.

Example

- Wither height in Berners
- Instead of measuring in inches we are going to classify short and tall.
- Define every dog over 26 inches as tall, everyone else is short
- The threshold for tall is 26 inches

Dog	A	B	C	D
Height	27	22	24	25
Height Class	Tall	Short	Short	Short

- In threshold traits we loose a lot of information

What have we learned so far?

- P=G+E
- Terminology/ Jargon
- Chromosomes/ Genes/ Locus/ Allele
- Homozygous/ Heterozygous
- Additive/ Dominant/ Recessive
- Stuff you did not learn in high school

What more have we learned so far?

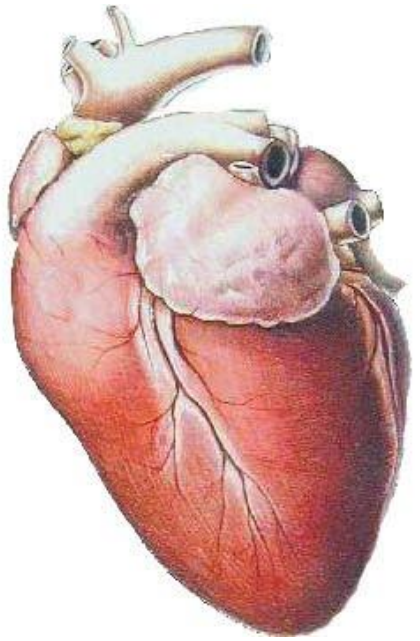
- Different types of Phenotypes
  - Single Gene Classifications (coat color)
  - Multiple Gene Continuous (height)
  - Multiple Gene Classifications -Threshold (disease)

- Each type of phenotype requires a different approach to improve.

Lets try to Improve the Phenotype through Genetics

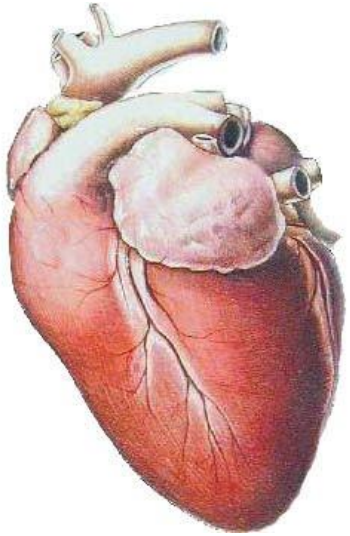
Heart Example

- Imagine the following situation:
  - There is a relative rare disorder in the dog population that causes a severe heart murmur. Dogs with this problem will die before they turn 2.
  - Studies on large groups of dogs show that the most likely mode of inheritance is single gene recessive.
  - The disease occurs in about 1 out of every 2500 dogs.

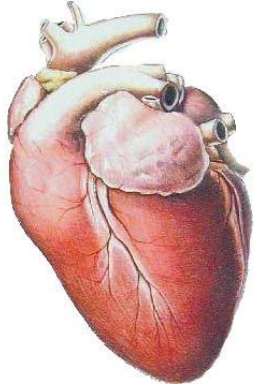


Heart Example

- You have a really good bitch that you want to breed.
- However, one of her full sibs died of the disease
- What would you do?
- Apply what you have learned.



Heart Example (Cntd)



- What information do we have?
  - There is a relative rare disorder in the dog population that causes a severe heart murmur. Dogs with this problem will die before they turn 2.
  - Studies on large groups of dogs show that the most likely mode of inheritance is single gene recessive.
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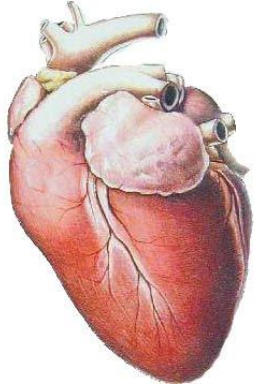
Heart Example (Cntd)



- What does it tell us?
  - There are two alleles H-healthy; h-murmur
  - HH and Hh dogs are healthy; hh dogs have the murmur
- What more?

Lets call the frequency of the h allele p

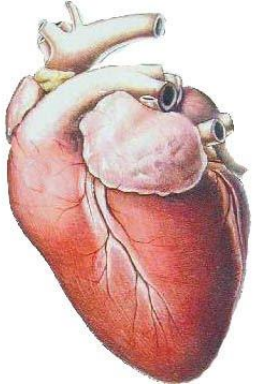
We know the frequency of hh = f(hh) = pp = p^2 = 0.0004 $\Rightarrow$ p=0.02

Similarly:

$f(HH) = (1-p)^2 = 0.98^2 = 0.96$

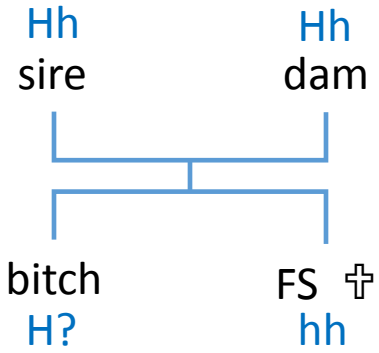
$f(Hh) = 2(1-p)p = 2\times0.98\times0.02 = 0.04$

If you choose a random dog from the population you have a 4% chance that it is a carrier of the murmur allele



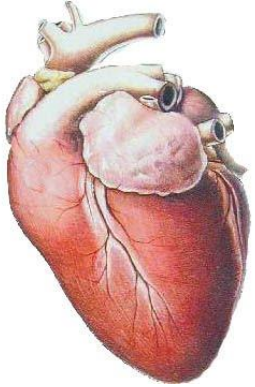
Heart Example (Cntd)

- What else do we know:
  - You have a really good bitch that you want to breed.
  - However, one of her full sibs has died of the disease.



- What is the chance that the bitch is Hh:
  - P(HH) = 0.5 × 0.5 = 0.25
  - P(Hh)= P(hH) + P(Hh) = 0.5 × 0.5 + 0.5 × 0.5 = 0.50
  - But we know that the bitch is not hh
  - P(Hh)=P(Hh)/(P(Hh)+P(HH)) = 0.50/(0.50+0.25) = 0.67
  - There is a 2/3 chance that she carries the allele

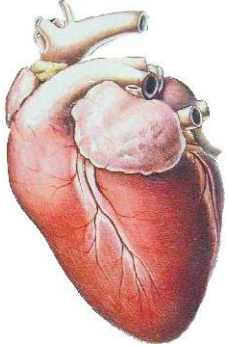
Heart Example (Cntd)



- What would you do?
  - The disorder is quite devastating.
  - There is a better than 67% chance that the bitch is a carrier.
  - A random male in the population has a 4% chance of being a carrier.

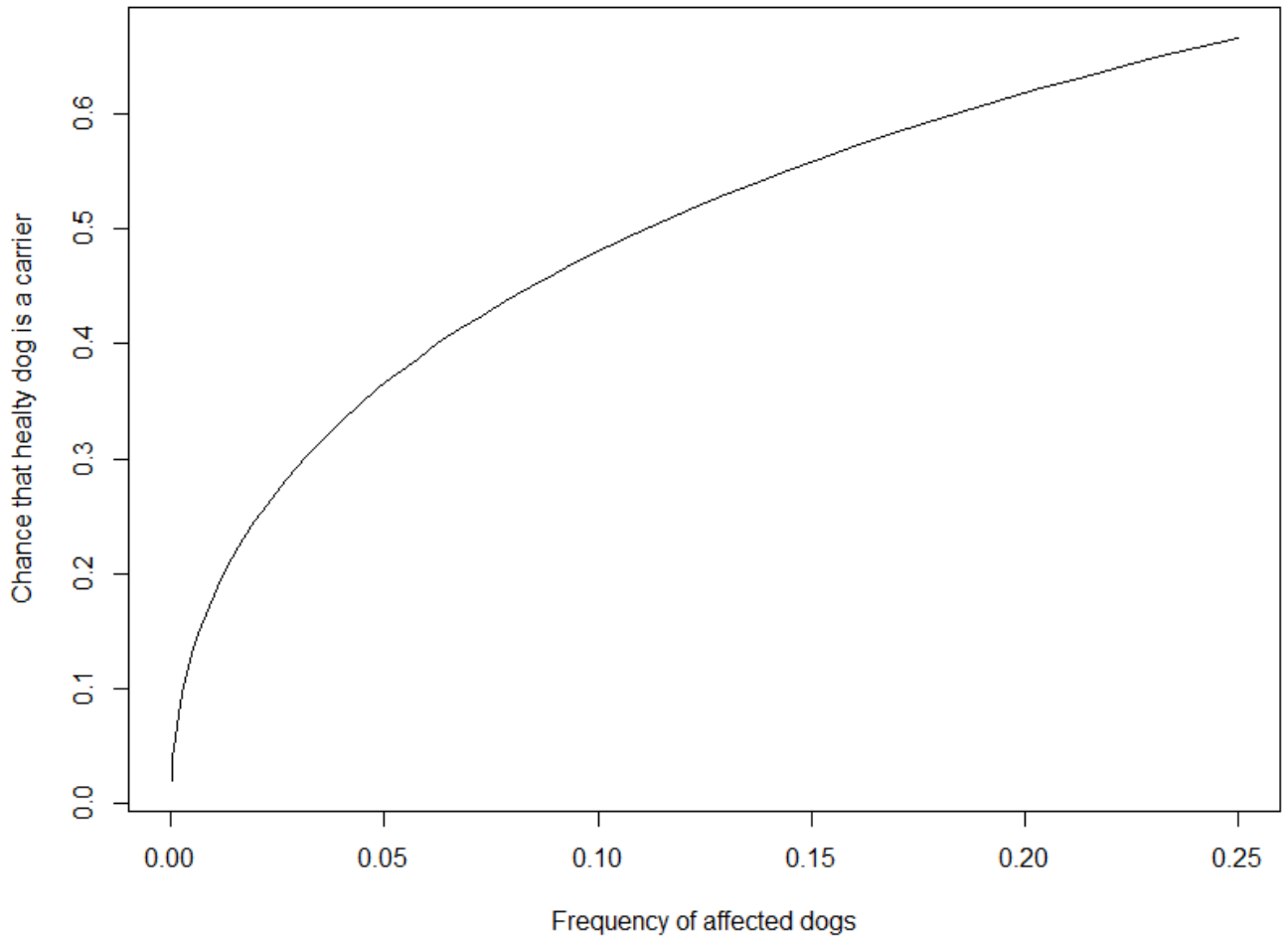
- There is no right or wrong answer, I would probably use the bitch and try to find a mate who has no close relatives with the disorder.
- Because affected dogs die before breeding age the chance of this allele going to high frequency in the population is quite small.
- With some smart breeding we can control the problem.

Heart Example (Cntd)

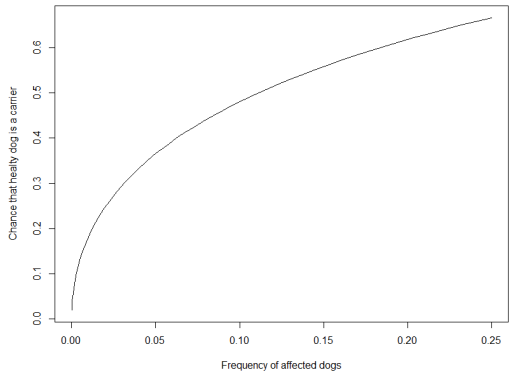


- What if the disease occurs in 1 in 16 dogs in the population?
  - $f(hh) = p^2 = 0.0625$ and $p = 0.25$
  - $f(Hh) = 2(1-p)p = 0.375$
  - $f(HH) = (1-p)^2 = 0.562$
  - Of all the healthy dogs $0.375/(0.375+0.562) = 0.40$ carry the h allele.
  - What would you do?

Relationship between the frequency of affected and the chance that a healthy dog is a carrier.



Relationship between the frequency of affected and the chance that a healthy dog is a carrier.



- Notice the sharp increase in the beginning of the graph.
- For f(aff) = 0.0025 $\Rightarrow$ P(carrier given healthy) = 0.10
- For f(aff) = 0.02 $\Rightarrow$ P(carrier given healthy) = 0.25
- You as a breeder have to decide what is acceptable.
- You can stack your deck by collecting additional information.

We Need a Genetic Test

It Will Take the Guessing Out of Breeding

Genetic Testing

- A genetic test is able to tell you the genotype of your dog at a certain locus.
  - HH
  - Hh
  - hh
- With this information you can find a compatible mate for your dog
- Of course the compatibility is only for that one locus.

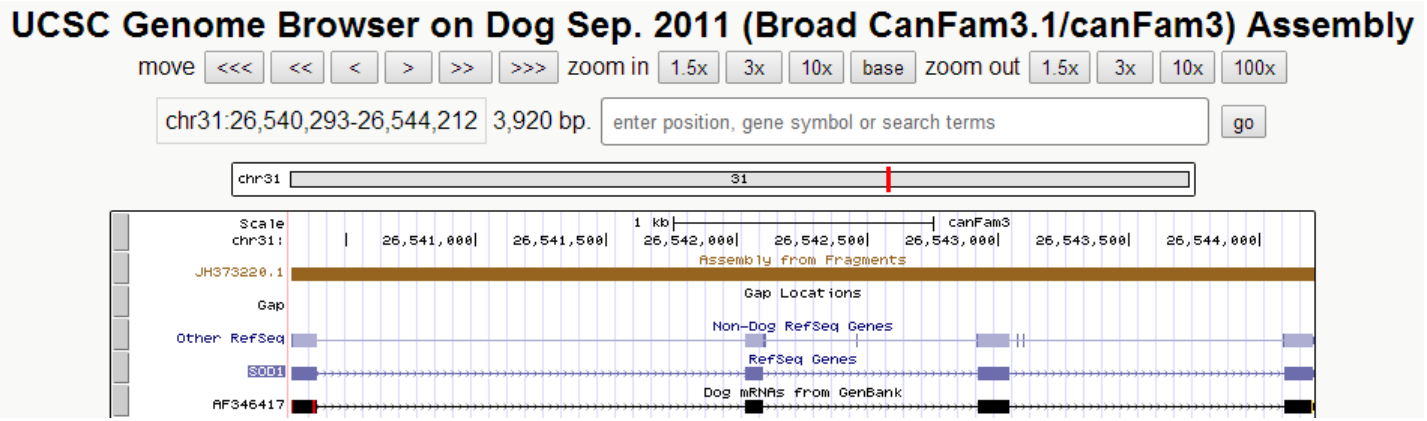
First Paper on Genetic Test for DM (PNAS 2009)

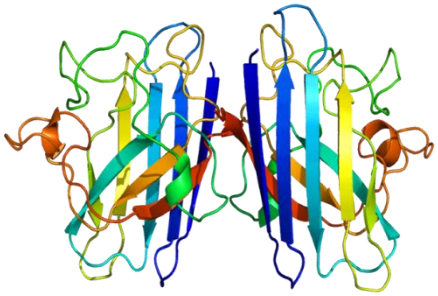
Genome-wide association analysis reveals a *SOD1* mutation in canine degenerative myelopathy that resembles amyotrophic lateral sclerosis

Tomoyuki Awano[a], Gary S. Johnson[a,1], Claire M. Wade[b,c], Martin L. Katz[a,d], Gayle C. Johnson[a], Jeremy F. Taylor[e], Michele Perloski[b], Tara Biagi[b], Izabella Baranowska[f], Sam Long[g], Philip A. March[h], Natasha J. Olby[i], G. Diane Shelton[j], Shahnawaz Khan[a], Dennis P. O'Brien[k], Kerstin Lindblad-Toh[b,l], and Joan R. Coates[k]

- Reported an association between a **missense** mutation and DM in dogs
- All affected dogs carried two copies of the mutation, none of the unaffected dogs did.
- Not all dogs that were homozygous for the mutation were affected
- Breed differences in mutation allele frequency
- Mutation has a **recessive** mode of inheritance and it had **incomplete penetrance**
- No BMD included in this study

SOD1 mutation





- SOD1 is on chromosome 31, missense mutation is in exon 2
- Early estimate of the allele frequency in BMD: 37% – 59%
- Recommendation:
  - Avoid breeding AA puppies (avoid NA×NA, NA×AA, AA×AA)
- BUT: there were some reports of AN dogs with DM

Second Paper

J Vet Intern Med 2014

Breed Distribution of *SOD1* Alleles Previously Associated with Canine Degenerative Myelopathy

R. Zeng, J.R. Coates, G.C. Johnson, L. Hansen, T. Awano, A. Kolicheski, E. Ivansson, M. Perloski, K. Lindblad-Toh, D.P. O'Brien, J. Guo, M.L. Katz, and G.S. Johnson

Allele frequency for the *SOD1.c118* mutation in BMD

#dogs	GG (NN)	GA (NA)	AA (AA)	f(A)
2413	941	1112	360	0.38

- Found 1 NN BMD and 2 NA BMD with confirmed DM
- The 1NN BMD was homozygous for a second missense mutation in *SOD1.c52T*
- *Now what???*

What do we know about the two SOD1 mutations in BMD

Table 2. Distribution of combined SOD1:c.52 and SOD1:c.118 genotypes in Bernese Mountain Dogs.

	SOD1:c118 Genotypes		
SOD1:c.52 Genotypes	G/G	G/A	A/A
A/A	316	399	136
A/T	35	24	0
T/T	2	0	0

- SOD1:c118 – f(A) = 0.38
- SOD1:c52 – f(T) = 0.03 – quite rare
- There is no evidence that the two mutations **segregate** together in the population.
- Fraction of carriers in the population
  - 61% for SOD1:c118
  - 7% for SOD1:c52

Another Analysis in this Paper
What is the risk of developing DM given the Genotype for the *SOD1:c118* mutation

Table 4. Owner reported online survey results for dogs that were sampled when clinically normal and younger than 8 years old, but were 10 years old or older when their clinical status was updated.

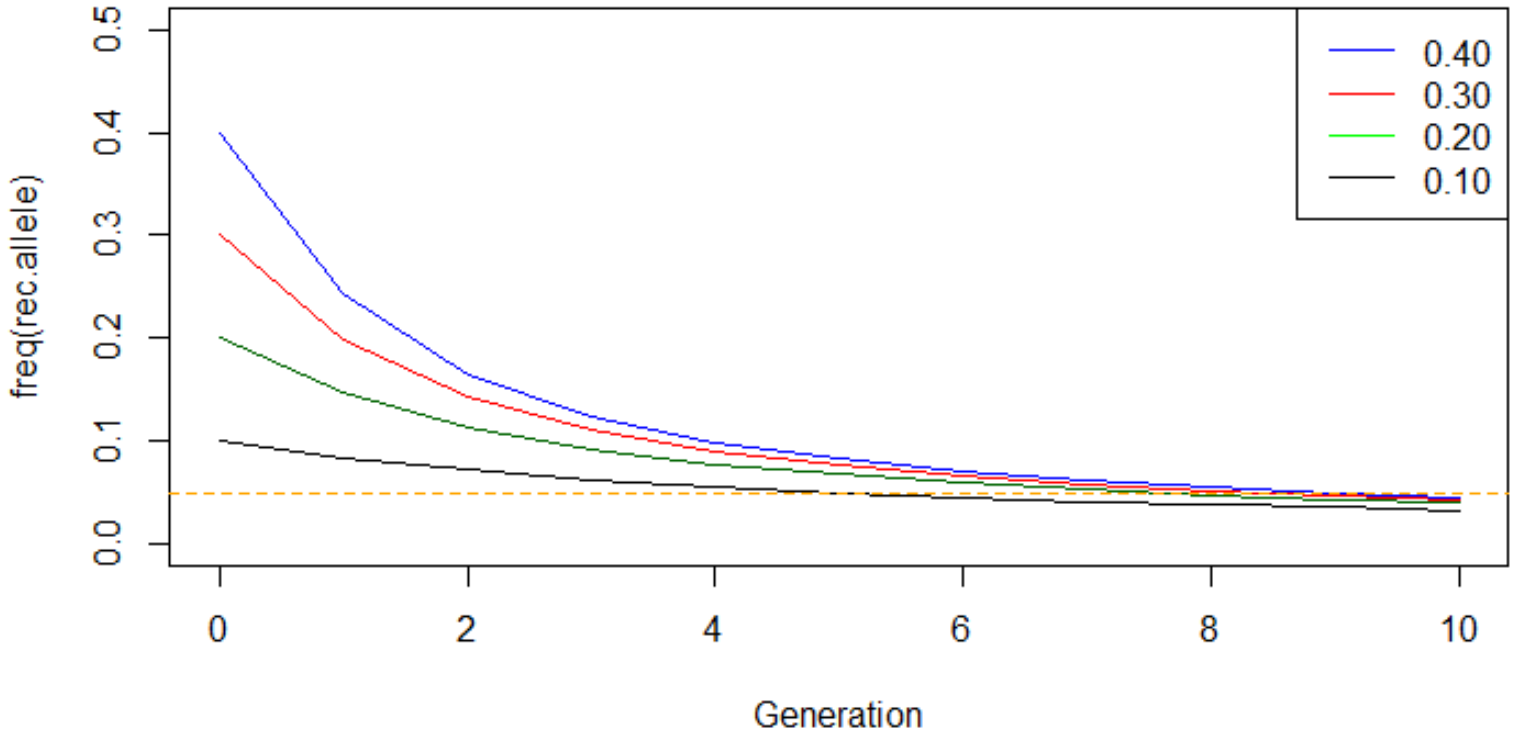
Genotype at *SOD1:c.118*	No. of Dogs Queried	No. of Queries Answered	Percent Response	No. Without Clinical DM Signs	No. with Clinical DM Signs	Percent with Clinical DM Signs
G/G	204	52	25	49	3	6
A/G	177	55	31	53	2	4
A/A	131	30	23	12	18	60
Total	512	137	27	124	23	19

- Over all breeds
- Risk of DM for NN and NA dogs about 5%
- Risk of DM for AA dogs was 60%

Recommendation for DM Breeding Strategy.

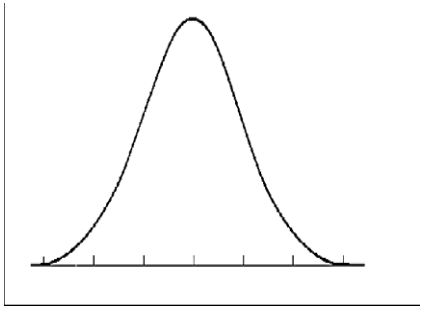
- From the paper: <snip> "strategy of breeding to avoid the production of SOD1:c118A homozygous puppies still appears to be warranted, particularly in breeds with high SOD1:c.118A allele frequencies where stricter selection strategies would come at the expense of selection for other important traits". <snip>
- Keep in mind: Right now there is no commercial test for genotyping the SOD1:c53T mutation.
- SSV is testing for this mutation

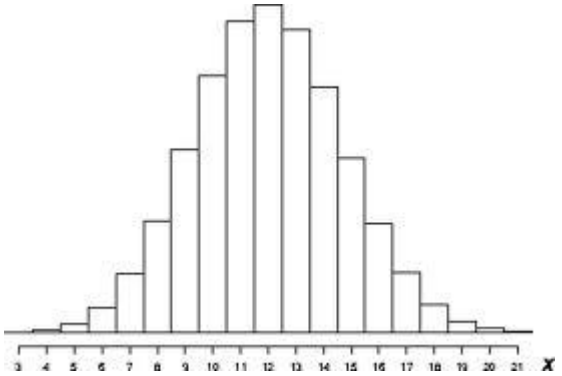
Breeding to Avoid Homozygous Carrier Puppies



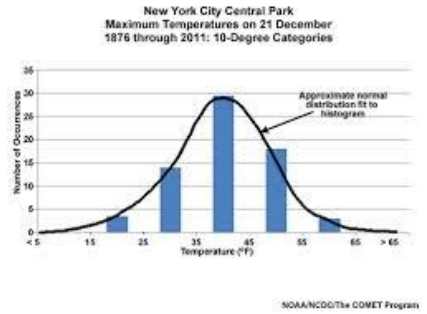
Quantitative Phenotypes

- These include phenotypes that are:
  - Continuous
  - Can be counted
  - Can be ordered from bad to good

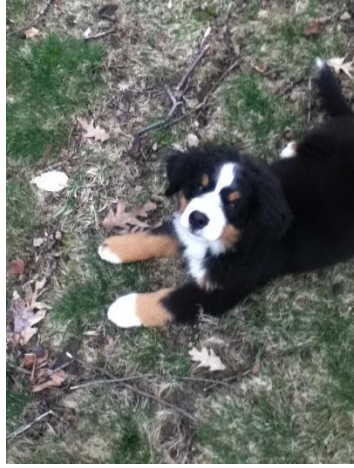




- Height, Weight, Age,
- # puppies
- OFA hip score, temperament



Continuous Phenotypes



$$P = G + E$$

- Phenotype tells us something about the genetics of the animal
- ***Heritability (h^2)*** expresses how much of the phenotypic difference are due to genetics.
- Low heritability – influence of genetics is low.
- High heritability – influence of genetics is high

Reported Heritability Various Breeds

Phenotype	Heritability Range (%)	Comments Low - high
Body Measurements	13-41	Chest Circumference – Wither Height
Hip Displaysia	14-58	Dependent on Method
Elbow Displaysia	11-31	Dependent on Method
Other Bone Problems	6-59	FCP-OCP
Eye Problems	13-59	Cataracts - PRA
Fertility	9-15	Fraction still born – rate of still born
Heart Problems	20-67	Cardiac murmurs
Behavior	0-31	Behavior towards strangers - hunting

Various sources through www.pubmed.gov with search terms: heritability estimate dog

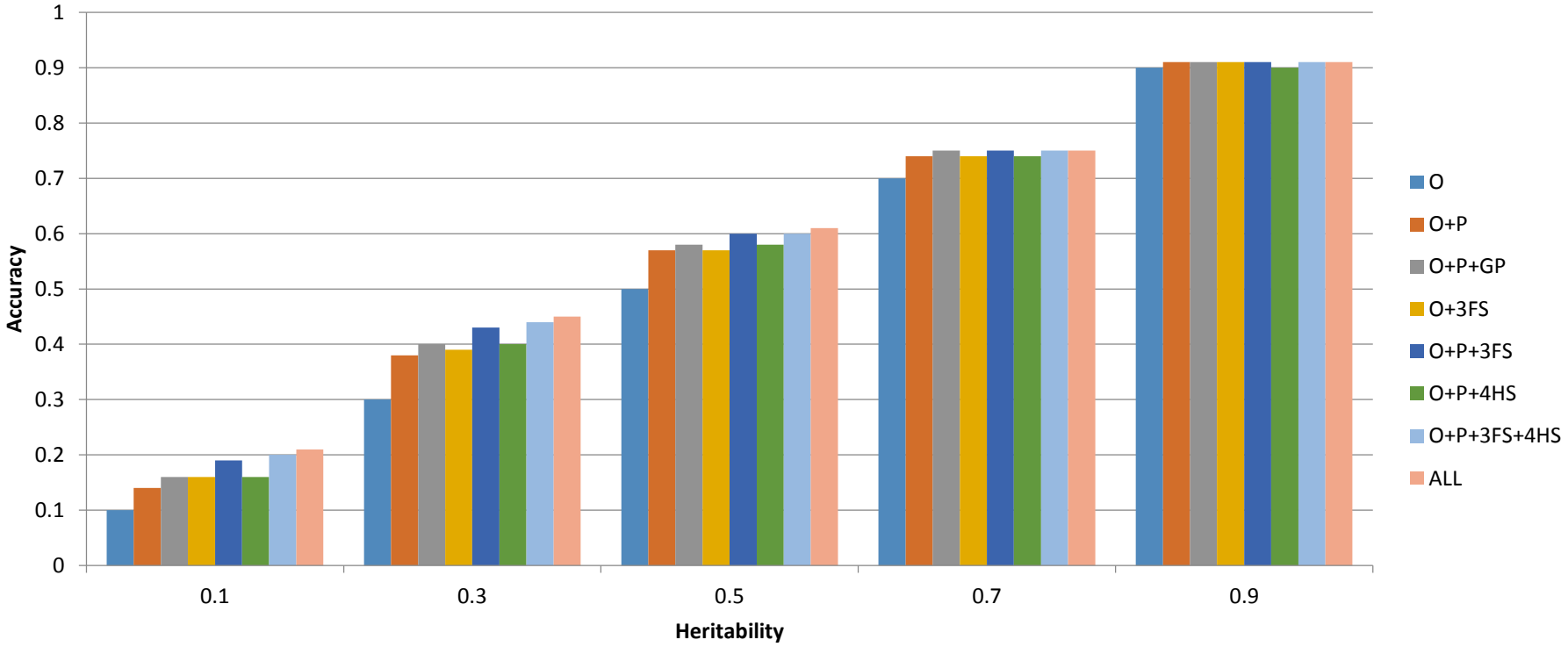
Berner Specific Heritabilities

Phenotype		Estimate	Source
CHD	Hip Dysplasia	26%	Hartmann et al., 2010
CED	Elbow Dysplasia	22%	Hartmann et al., 2010
OCD	Osteochondrosis Dissecans of the Humeral Head	0.40	Hartmann et al., 2010
FCP	Fragmented Coronoid Process	0.59	Hartmann et al., 2010
FCP	Fragmented Coronoid Process	0.06	Lavrijsen et al., 2012

What Information to Use when Selecting Mates

- Use dog's own performance
- Take a look at litter mates
- Use information on parents
- Use information on grand-parents
- Cousins
- Second cousin twice removed
- Etc.
- Can't see the tree in the forest

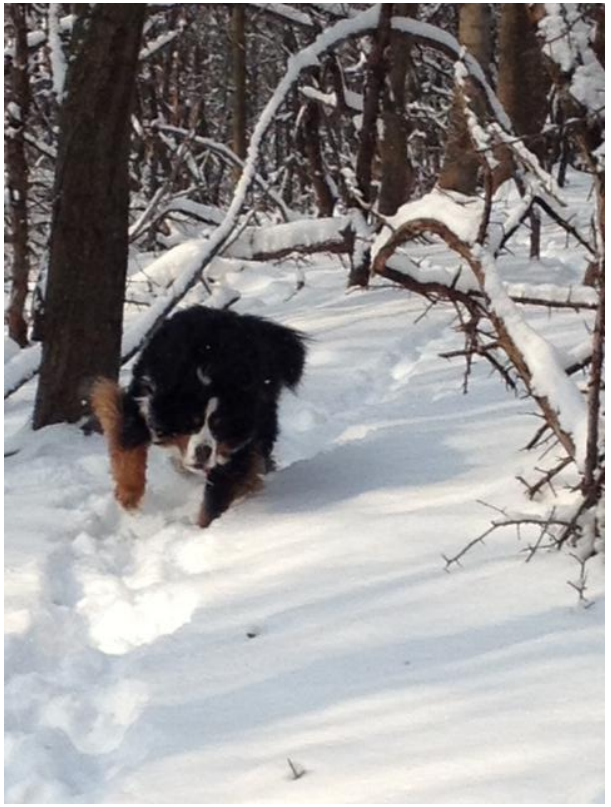
What is the Value of the Different Sources of Information



- For low heritabilities additional information can almost double the accuarcy
- Information on relatives carries very little value for higher heritabilities
- Information on 3 FS is as valuable as the information on parents and 4 HS
- Keeping records is important, especially for low heritability traits

Example OFA Hip scores

1. Severe Dysplastic
2. Moderate Dysplastic
3. Mild Dysplastic
4. Borderline
5. Fair
6. Good
7. Excellent



Assume that the average score is 4

Which is the Better Mate Example 1

- A good dog in a bad litter or a bad dog in a good litter?

Dog	Potential	FS1	FS2	FS3
Mate 1	6	3	2	3
Mate 2	3	6	7	6

Approximate Estimated Breeding Values

heritability	Mate 1	Mate 2
0.10	0.02	0.10
0.30	0.18	0.07
0.50	0.48	-0.19

Relatives are more important for traits with low heritability

Which is the Better Mate Example 2

- A good dog with no relative information versus an average dog with good parents?

Dog	Potential	Sire	Dam
Mate 1	7		
Mate 2	3	7	7

Approximate Estimated Breeding Values

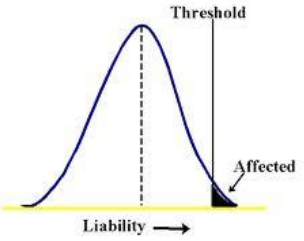
heritability	Mate 1	Mate 2
0.10	0.70	0.92
0.30	2.10	2.34
0.50	3.50	3.29

Relatives are more important for traits with low heritability

Treshold Traits

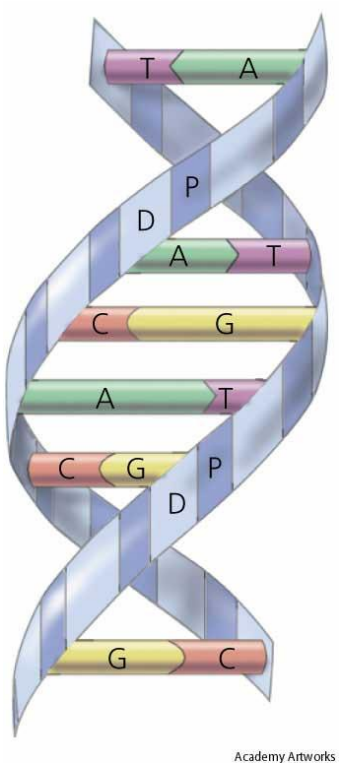
- Unfortunately not all phenotypes have a nice continuous outcome.
- Many polygenic phenotypes have an affected/unaffected, yes/no, or 0/1, outcome.
- This is also known as a binary outcome.
- We think of these as phenotypes with an underlying continuous (liability) distribution.
- When the underlying trait passes a certain treshold the dog becomes affected.

What is a Breeder to do?



- When dealing with these traits think about the underlying liability.
- Level of heritability plays a role in whether an affected dog can be used in a breeding program.
- Think, low heritability and none of the relatives is affected.
- In general very little is known about the genetics of these traits.

Genetic Test to the Rescue



Treshold Traits

- When we know the loci and genes we can estimate the genetic value of an animal.
- This is what is being developed by Catherine Bourdain, Benoit Hedan, Heidi Parker,Elaine Ostrander and others.
- Partially funded by Berner owners.

Histiosarcoma

Published OnlineFirst May 23, 2012; DOI: 10.1158/1055-9965.EPI-12-0190-T

Cancer Epidemiology, Biomarkers & Prevention

Research Article

The *MTAP-CDKN2A* Locus Confers Susceptibility to a Naturally Occurring Canine Cancer

Abigail L. Shearin[1,2], Benoit Hedan[3,7], Edouard Cadieu[1], Suzanne A. Erich[4], Emmett V. Schmidt[1,6], Daniel L. Faden[1,2], John Cullen[7], Jerome Abadie[9], Erika M. Kwon[1], Andrea Gröne[5], Patrick Devauchelle[10], Maud Rimbault[1], Danielle M. Karyadi[1], Mary Lynch[6], Francis Galibert[3], Matthew Breen[7,8,11], Gerard R. Rutteman[4], Catherine André[3], Heidi G. Parker[1], and Elaine A. Ostrander[1]

Results

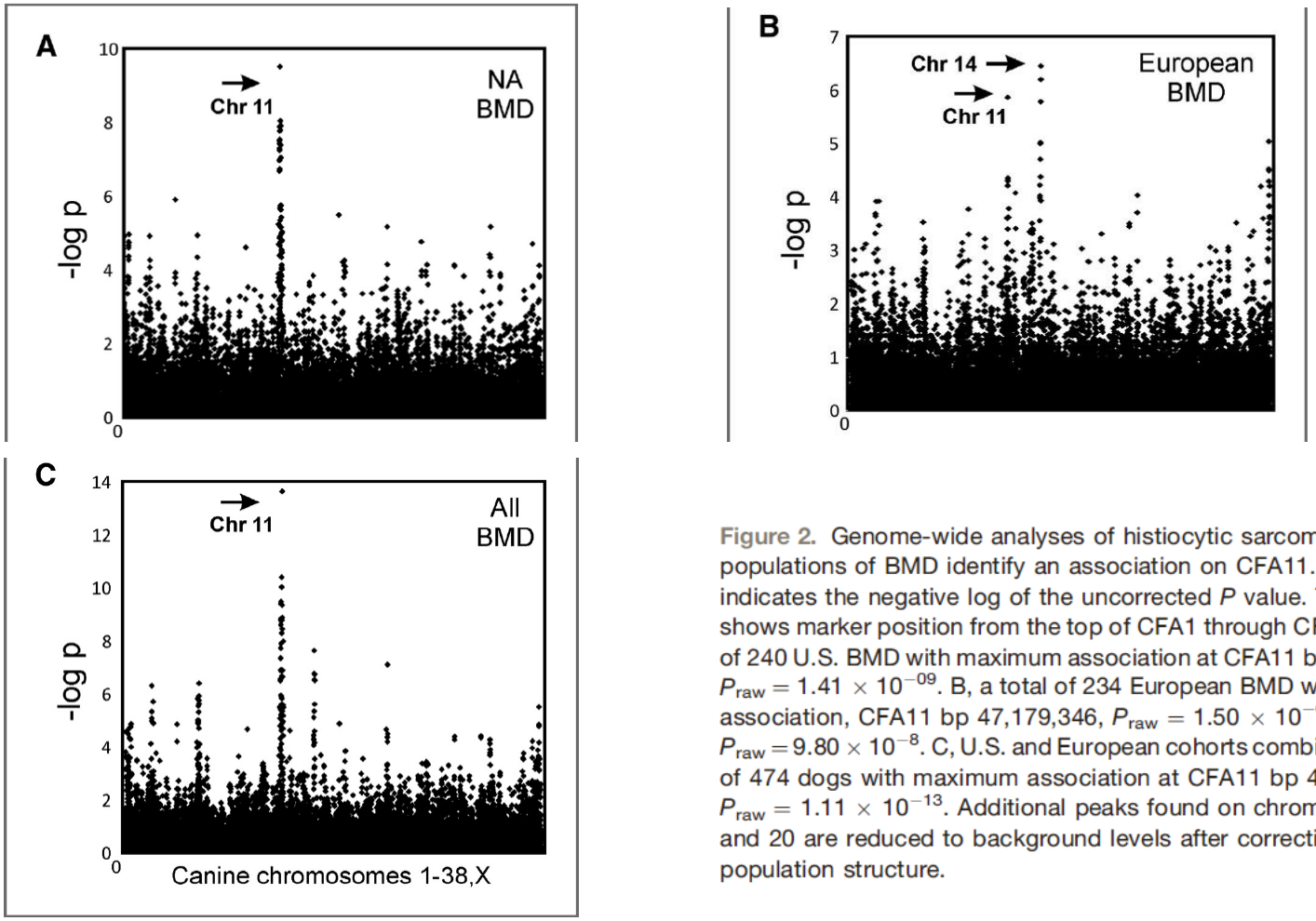


Figure 2. Genome-wide analyses of histiocytic sarcoma in 2 populations of BMD identify an association on CFA11. The Y-axis indicates the negative log of the uncorrected *P* value. The X- axis shows marker position from the top of CFA1 through CFAX. A, a total of 240 U.S. BMD with maximum association at CFA11 bp 41,359,032, $P_{raw} = 1.41 \times 10^{-09}$. B, a total of 234 European BMD with 2 peaks of association, CFA11 bp 47,179,346, $P_{raw} = 1.50 \times 10^{-6}$ and CFA14, $P_{raw} = 9.80 \times 10^{-8}$. C, U.S. and European cohorts combined for a total of 474 dogs with maximum association at CFA11 bp 47,179,346, $P_{raw} = 1.11 \times 10^{-13}$. Additional peaks found on chromosomes 2, 5, and 20 are reduced to background levels after correcting for population structure.

Since Then

Think genetics

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Memorandum agreement
Histiocytic Sarcoma Questionnaire

Histiocytic Sarcoma Pre-Test

A genetic tool to aid in selection is available to breeders

Research in Histiocytic Sarcoma in the Bernese Mountain Dog is progressing

More info

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To enable breeders to benefit from the preliminary results of the research on Histiocytic Sarcoma in the Bernese Mountain Dog, the ANTAGENE laboratory, in collaboration with the CRNS Canine Genetics Team in Rennes, has developed a genetic pre-test.

The pre-test for Histiocytic Sarcoma gives results expressed as a genetic index which is based on the statistical analysis of genetic markers from the research data. It is a **selection tool** and **does not constitute a predictive test for the development of this cancer**. The pre-test for Histiocytic Sarcoma is a genetic tool to assist breeders in the management of their kennels and decisions on matings to enable them to reduce the incidence of histiocytic sarcoma in the population of Bernese Mountain Dogs.

The genetic index is based on nine genetic markers (panel SH0912) identified from scientific research on Histiocytic Sarcoma in the Bernese Mountain Dog.

The calculation of the index has been developed from a population of 1081 European dogs, mainly from France.

- **The pre-test for Histiocytic Sarcoma has three possible results expressed as an index :**

Indice	Explication
A	The individuals tested have four times the chance of NOT developing Histiocytic Sarcoma.
B	Neutral index
C	The individuals tested have four times the risk of developing Histiocytic Sarcoma. The risk of the markers associated with the disease being transmitted to offspring is greatly increased.

Histiosarcoma Pre-test

- **Advice to breeders on the use of the index**

It is important within a breeding population to give priority to individuals with the best index but is also of the utmost importance when selecting breeding pairs that sufficient genetic diversity is maintained in the breed. This genetic pre-test should be just one of the many selection criteria.

- **Recommendations**

An Index C dog with a number of other positive qualities should not be removed from the breeding programme, rather it should only be mated with individuals showing Index A or B results. Mating programmes should be planned to avoid C x C matings.

Being a selection tool, the SH pre-test is only available to breeders.

The Test

- Counts the number of risk alleles over the 9 markers – gene score
- Classifies the gene score in A, B and C
  - A animals have 4 fold reduced chance of not developing HS
  - C animals have 4 fold increased chance of developing HS
  - B animals have neutral index

Advice to Breeders

- Do not remove C animals from the breeding population
- ***However, do not breed C to C***
- Animals with the best index should be used for breeding.
- One has to main diversity in the breed.
- The pre-test should be one of many tools when selecting animals

Clean-up Stuff

Different Researchers use Chromosomal Information Differently

- One group looks at the genetics that a dog is born with to predict the risk of developing diseases.
- They try to pinpoint the mutation that causes the disease.
- Mutations that are identified are found in all cells.
- This information can be used by breeders to breed dogs with lower disease risk.

Cancer Researchers

- Compare normal cells and cancer cells to check for chromosomal differences.

- The dog is born with normal cells.
- A mutation caused a cell to divide abnormally
- A cancer can grow.
- All other cells are still normal.

- The mutation is only found in the cancer cells.
- The information can be used to target treatments.

Breeding Programs

- Every breeding program needs a Breeding Goal.
- Stick with this Breeding Goal for many generations.
- Expect that you will not reach your Breeding Goal in one breeding.
- Some breedings will lead you away from your goal

Breeding Goals

- What information do I need to get to my goal?
- How should I use this information to get to my goal?
- Pick two or three well defined traits that you want to improve the most.
  - When picking too many things to improve you will not make progress in any of them.
- For all other traits cull out the really bad dogs.

Genetic Testing

- More genetic tests will become available.
- Just because they are available does not mean you should use them in your breeding decisions.
- Is the trait important?
  - Importance does mean different things for different people.
- Can I breed around the problem without causing a major genetic bottle neck.


DEL MONTE FOODS