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Teaching Genetic Principles with Dogs

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We developed a collection of genetics teaching resources using dogs as a comprehensive model. Dogs are familiar, have traits that can be scored from photos or direct observation, and alleles with varied inheritance patterns. Specific proteins underlying many of their distinctive physical features have been identified, which helps students connect molecules to genotypes and mutations to phenotypes. Instructors can use our existing handouts, problems, and cases, as well as design new genetics problems for their students, then publish their materials in a growing open-source content library and get feedback from other users.

Keywords: genetics, word problems, model organism, teaching resource, dogs

Introduction

Many students who enroll in our sophomore-level genetics course say they already understand and can apply basic genetic principles, which they learned in freshman coursework or an advanced biology course taken in high school. Yet data from pre/post and standardized tests, responses on course evaluations, and anecdotal reports from instructors all indicate that the majority of students have a quite fragmented understanding of genetics when they enter the course. Even after completing the basic genetics course, many students still struggle to transfer and apply principles of gene regulation and function to upper-level coursework (*ADJ-personal obs*.). This problem is not unique to us. Nationally, students taking the 2013 AP Biology Exam scored 56-63% correct on the exam overall, but 48-55% correct on questions relating to genetics, molecular biology, and application of mathematics to biology (College Board, 2013.)

We believe students struggle to master genetics (at least in part) due to cognitive overload. According to cognitive load theory: 1) all learners have a finite amount of processing capacity, and 2) each learning task demands part of that processing capacity (Schumacher, 2013.) Imagine a lab exercise in which students must sort and score F2 offspring from a Drosophila test cross. They must coordinate several previous and current tasks or skills:

- Using a dissecting microscope (Task 1), identify and extract phenotypic information about an unfamiliar model organism (Task 2).
- Compare observed phenotypes (Task 3) to inheritance patterns memorized previously (Task 4).
- Choose a mathematical method (Task 5) and compare their results to predictions (Task 6).

Even this simple example has 6 tasks for students to manage, which can easily exceed their cognitive load capacity. Using a more familiar organism can reduce or eliminate the first two tasks.

A second reason students struggle with genetics is they are not deeply engaged by the model organisms. In Bybee's 5E model of instructional design, engagement is the critical first step in meaningful learning (Tanner, 2010). Fruit flies, nematodes, annual plants, and genetically modified mice are powerful research tools, but lay outside of students' common experience. A model organism that is part of their personal lives is more likely to engage and maintain interest.

In 2012 we launched a web-based instructional resources project called Teaching Genetics With Dogs (abbreviated TGWD) (**http://www.adapaproject.org/doggenetics/**). It provides instructors with:

- Links to numerous excellent existing resources created by others,
- Specific guide materials for students,
- A library of classroom-tested genetics problems, and
- Resources they need to write new problems, and share them with others.

Why Dogs?

Dogs have many benefits as teaching models. We share 15,000+ years of evolutionary history, our homes, and our daily lives with them. That familiarity reduces the overall cognitive load that students experience. Dogs trigger strong emotional connections, so are more likely to engage students. In addition, class lessons are reinforced every time students walk by a purebred dog or a mixed terrier on campus.

In the past 20 years dogs have become a major model for human disease genetics. There are numerous examples from dogs (all with direct applications to humans) that instructors can use to teach DNA regulation and mutation mechanisms, medical genomics, population genetics, phylogenetic reconstruction, and quantitative trait loci mapping. Geneticists have identified many of the genes responsible for a dog's observable features, and described in detail how corresponding alleles and proteins determine canine morphology, physiology, intelligence, and behavior. We expect that making this information available to students can help them better understand the connections between genotype, protein activity, and phenotype.

Dogs have one more benefit that few other genetics teaching models do: students can contribute their own materials to the curriculum. Any student with a cell phone or camera can bring in photos of dogs for their classmates to evaluate.

The Student Outline

The **Student Outline** is not a set of specific exercises, but rather an example of how instructors can incorporate resources from the TGWD site into an undergraduate genetics course. The outline includes:

- An introduction to dogs as genetics models.
- A guide to canine genetic nomenclature (helpful when reading primary literature.)
- Two standardized evaluation guides, one for body and coat structure phenotypes, the other for coat color phenotypes.
- An overview of genes controlling body morphology, the alleles, and the phenotypes.
- An overview of genes controlling coat color, the alleles, and the phenotypes.
- Four sample word problems.

Students would receive the handouts at the start of a course or lab. Instructors can post the handouts to their own website, or point students to the TGWD website to read them online. Black-and-white photocopies are not advised; each handout has several color photographs of the phenotypes.

Using the guides and information in the handouts, students should be able to solve all four problems by the end of a typical undergraduate genetics course. The first three problems would be assigned at different times during the semester as students developed the necessary skills and knowledge to solve them. The fourth problem is a stacked series that revisits the same dog several times over a semester, each time posing a more complex question. Answer keys and author and image credits for all four problems are in **Appendix A**.

The **Notes for the Instructor** explains how to request access to the complete TGWD Resources Catalog, and outlines different options for incorporating TGWD materials into coursework.

Student Outline

Introduction

Why Use Dogs to Study Genetics?

Since Thomas Hunt Morgan found his first white-eyed fruit fly in 1910, scientists have used many different organisms as models for studying genetics. Among the models are fruit flies (*Drosophila melanogaster*), mold (*Neurospora crassa*), beer and bread yeast (*Saccharomyces cerevisiae*), roundworms (*Caenorhabditis elegans*), bacteria (*Escherichia coli* and others), various viruses, mice (*Mus musculus*), and mouse-ear cress (*Arabidopsis thaliana*). Dogs have long been used as research models for physiology, endocrinology, and cancer research, but not for studying genetics. This has changed in the past 20 years or so though.

Shortly after The Human Genome Project completed its first draft, project teams began sequencing genomes of other model organisms. As additional genomes were published, geneticists compared them to our genome. They were surprised to discover that dogs (*Canis familiaris*) have many (some say most) of the same gene-related diseases as people (Shearin, 2010.)

Dogs have many advantages as genetic models of human diseases. Mice and other organisms must be genetically manipulated, bred or selected to get strains that mimic human disease. Hundreds of dog breeds exist today, and the most common diseases for each breed are well documented (for an example, look at the AKC Canine Health Foundation's database at **http://www.akcchf.org/canine-health/breed-specific-concerns/**). Additionally, most purebred dogs have **pedigrees** (extended family trees) with detailed information about the dogs that were mated in each generation. These pedigrees make the task of mapping disease inheritance patterns much simpler.

For example, researchers long searched for the gene(s) responsible for narcolepsy, a human neurological condition where sufferers become paralyzed and appear to fall asleep when they get too excited. Geneticists found that a few purebred Doberman pinschers and dachshunds develop narcolepsy (Lin, 1999.) Using those dogs' pedigrees as their starting point they traced the genetic defect to a mutant hypocretin receptor. A year later, the same lab showed that the mutant receptor also causes narcolepsy in humans (Nishino, 2000.) (You can watch videos of the narcoleptic dogs at **http://youtu.be/R6_hwbp97eU** and **http://youtu.be/nvMyuZKGKAY**.)

Dogs are good models for basic genetics too. Unlike flies, you can score most phenotypes by eye, even from photos. Geneticists already know many of the specific genes, alleles, and proteins that determine dog morphology, physiology, intelligence, behavior, and disease susceptibility. When you know how a protein works normally, you can predict how mutations to the DNA that codes for that protein will affect the dog's phenotype.

Using These Handouts

You will be given several handouts that explain which genes control a dog's overall body shape, coat structure, coat color, and other phenotypes. They also outline some standard strategies for evaluating phenotypes.

This semester you will be assigned several sets of genetics word problems. To solve them you must apply the genetic principles you will learn in class, and use the information in these handouts. The questions you will see on course exams will be similar to the word problems you will be assigned.

You will be referring back to these handouts regularly, so put them somewhere they are easily accessible.

Handout #1: Standard Genetic Nomenclature for Dogs

How Do We Describe Genes in Dogs

Dogs have 38 autosomes plus either XX or XY as Pair 39. In this class we will be using the same nomenclature that geneticists use in research publications. Most research papers use the notation "CFA ##" to indicate which chromosome a gene is located on. CFA is short for *Canis familiaris*, and "##" indicates the chromosome.

Like most genetic notation, we use single letters (or sometimes two letters) to identify genes. Uppercase letters indicate alleles with dominant inheritance patterns, and lowercase letters indicate traits with recessive inheritance patterns. Here are some examples of the standard notation format.

Specific Examples

CFA 5: E/E

This notation means the E locus is on Chromosome 5, and the dog described is homozygous for the dominant (E) allele.

CFA 5: E/e

This dog is heterozygous for locus E on Chromosome 5. It carries both dominant (E) and recessive (e) alleles for this locus.

CFA 5: e/e

The dog described is homozygous for the recessive (e) allele for the E locus.

E/-

This annotation is used to describe phenotypes, or if we do not know the complete genotype. Again, E indicates that the dog displays the dominant phenotype, but based on the given information or its appearance, we cannot say whether the dog is E/E, or E/e.

Notice that in this example, the chromosome # has been left off. It is not required if the reader is expected to know it already, or it is not essential for understanding which genes are involved.

E^{M}/E

In dogs there are some loci with multiple dominant alleles. The superscript in this annotation simply indicates an alternative dominant allele for the E locus.

a^{y}/a

There are some loci with multiple recessive alleles. The superscript in this annotation simply indicates that this dog has inherited two different alleles for the agouti (a) locus. Both the ay and a alleles behave as recessives.

Handout #2: Evaluating Body and Coat Structure Phenotypes

To evaluate a dog's genetically controlled traits, you need to know what phenotypes the dog shows. This list of standard questions is adapted from Alderton's *Dogs* (Alderton, 1993.) It is a quick yet complete overview of all the major phenotypes that can identify specific characteristics reliably and consistently. Not all questions need to be answered; many single-gene phenotypes (which are marked) can be identified by a single question.

General Physical Features

1. What is the dog's height, measured at the dog's withers (shoulders)?

   Generally:
   - Large and extra-large dogs are >24 inches
   - Medium dogs are 18-24 inches
   - Small dogs are <18 inches.

   Small overall size in dogs has been linked to specific alleles for several different genes. All of the alleles decrease insulin-like growth factor 1 (IGF-1) signaling in some way. The opposite has not been reported: IGF-1 is not over-produced in large dogs (Sutter, 2007)

Size differences in dogs.

1. Dogs have the most extreme within-species variation of any mammal, as shown by this wolf-hound and chihuahua.
2. A great Dane, an example of a large breed.
3. Airedale, and example of a medium sized breed. Though still a good-sized dog, Airedales have reduced IGF-1 activity.
4. Pomeranian, a small breed. They are small because of reduced IGF-1 activity.

2. What is the shape of the dog's head?

   - Nose is long, skull is narrow (Jack Russell terrier, afghan hound, greyhound)
   - Skull shape is average (i.e., wolf-like) (German shepherd, golden retriever)
   - Skull is strongly rounded, with relatively short nose (chihuahua, beagle, Labrador retriever, chow)
   - Skull is angular, square, or blocky (mastiff, St. Bernard, rottweiler)
   - Nose is strongly blunted or tucked under skull (brachycephalic) (pug, bulldog, Boston terrier, boxer)

   Brachycephaly has been tentatively linked to a single gene or small group of genes. Other head shapes appear to be the result of multiple genes. (Bannasch, 2010; Schoenebeck, 2012; Schoenebeck, 2013).

Differences in head shapes:

1. German shepherd
2. Yellow Labrador retriever
3. Rottweiler
4. Bulldog

3. Does the dog have long or short legs? (Single gene)

   - Legs are about as long as the overall body length (wild type seen in most dogs)
   - Legs are much shorter that overall body length (Dachshunds, basset hounds)

   Foreshortened legs in dogs is a form of achondroplastic dwarfism. It is caused by an autosomal dominant allele of fibroblast growth factor 4 (FGF-4) retrogene (Parker, 2009.)

Long versus short legs. The beagle (1) has long legs whereas the dachshund (2) has foreshortened legs.

4. What is the coat structure and texture?

   - Overall hair length on back and ribs: short vs. long (Single gene)
   - Hair texture: flat (also called smooth), fluffy, or wiry (Single gene)
   - Undercoat (soft hairs beneath a heavier topcoat): present or absent
   - Hair is straight versus curly (Single gene)

   Coat length is controlled by FGF-5. Coat texture is controlled by R-spondin 2 and keratin-71 (Cadieu, 2009.)

A comparison of different coat structures and textures.

1. The beagle has short straight hair
2. A schnauzer has short wiry hair
3. The husky has long straight hair and a double coat
4. The puli has long, curly hair.

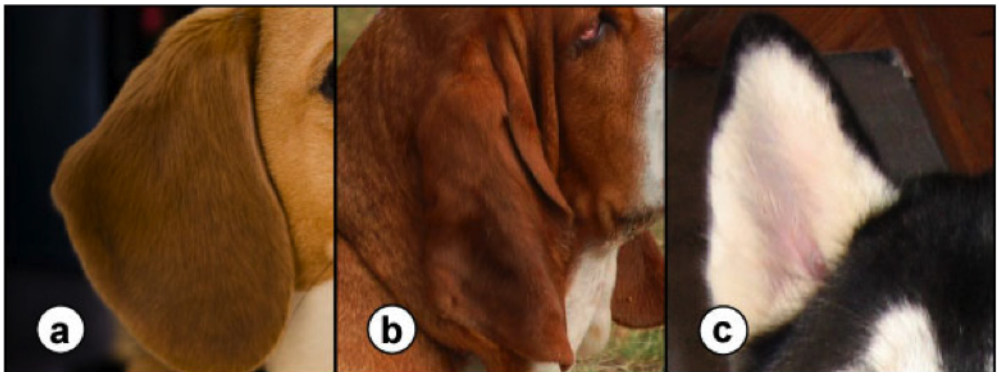
5. Does the dog's face have furnishings (a moustache or extended eyebrows)? (Single gene)
    - Absent (most dogs)
    - Present (schnauzers, shih tzus)

    Furnishings are controlled by R-spondin-2 (Cadieu, 2009.)

Like most dogs, the Beagle (1) has no furnishings whereas the Schnauzer (2) has a mustache and extended eyebrows.

6. What is the natural shape (not docked or altered) of the ears?
    - Overall size relative to head?
    - Position? (Hanging versus erect; straight versus folded)

    Evidence suggests ear shape is controlled by multiple genes (Boyko, 2010).

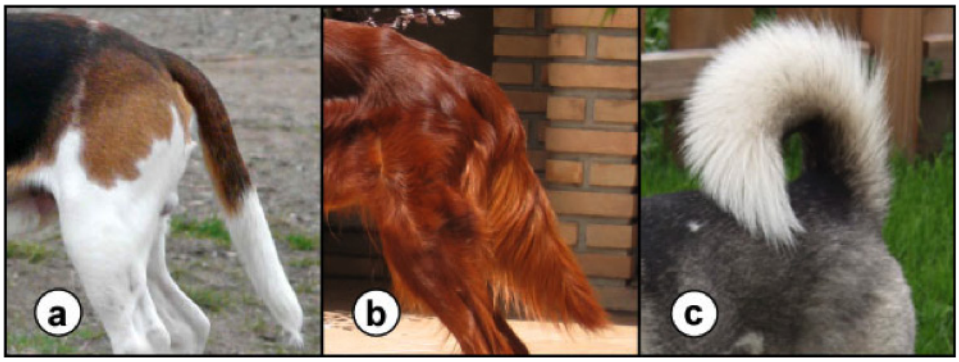


Various dog ears.
A. A beagle's ear, neatly folded near the head.
B. A basset hound's ear, draping and pendulous (like a curtain),
C. A husky's ear, pointed and held erect.

7. What is the natural structure of the tail (not docked or altered)?

- Length relative to torso length?
- Relative curl? (On scale of 1 (straight like a beagle) to 5 (tightly curled like a spitz))
- Decoration: plain (beagle, Labrador retriever) or feathered beneath, with hair hanging down (setters and gun dogs)?

Tail length and curl are both multi-gene traits (Boyko, 2010.)



Dog tails.
A. A beagle has a plain straight tail
B. Setters have straight, feathered tails
C. Huskies have a curled tail, found in most "spitz-type" dogs.

Coat and Eye Color

Inheritance of coat color is hard to understand and map out because multiple interacting genes are involved. However, the relevant genes still follow well-defined inheritance rules. If you learn and understand the cell biology underlying coat colors first, the inheritance patterns make more sense.

The questions below help you **categorize** general color reliably. Remember, this handout is just to help you identify the phenotypes. To determine the inheritance patterns, you need to refer to Handout #5: Genes Controlling Coat Color.

8. Which basic coat colors are present? A dog's coat color can have up to 6 distinct "major pigment colors". These are:

- Pure black
- Milk chocolate brown
- Various shades of gray (slate or blue-gray, neutral gray, or brown-grey in color; pale silver to charcoal grey)
- Yellow (ranges from very pale cream to fawn gold, or deep brown-orange)
- Red (ranges from pale peach to dark red, or red-brown (liver colored))
- Pure white (i.e., absence of pigment)

The six major pigment colors in dogs.
A. Black Schipperke.
B. Brown (chocolate) Labrador retriever.
C. Grey Weimaraner.
D. Yellow Labrador retriever.
E. Red Irish setter.
F. White Samoyed.

9. Is the coat one color, or many colors? If many, which color predominates?

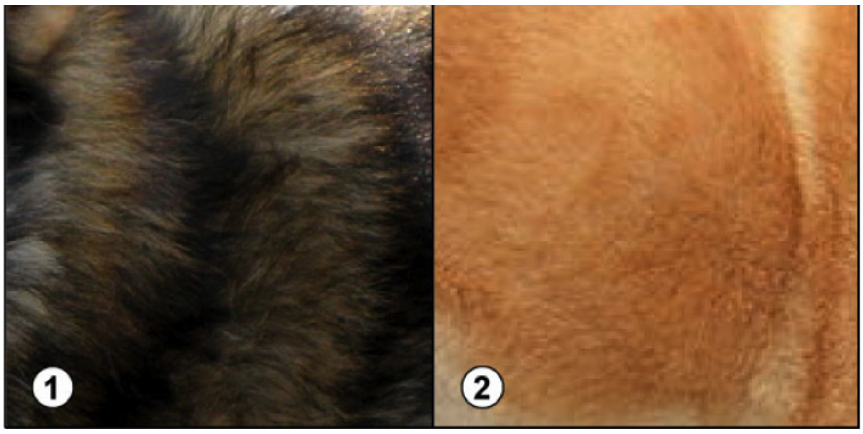
   To choose the dominant color, **focus on a dog's back and ribcage behind its front legs**. The color on a dog's chest, head, feet, and tail is less consistent.

A tri-colored rough-coated collie. This collie is predominately black on its back and shoulders. The reddish-orange borders and white underside are secondary colors.

10. Are individual hairs multi-colored?

- No; individual hairs are one solid color for their entire length
- Yes; individual hairs change color from base to tip.

Having **individual hairs** that have alternating bands of eumelanin (black/grey/chocolate brown color) and pheomelanin (blond/yellow/red color) is called an **agouti** phenotype. Agouti coloration is controlled by a single gene, but it can be covered up by other genes.



A comparison of coats with banded agouti hairs (1) versus yellow hairs (2).

11. Are both eyes the same color?

- Yes; both eyes blue, or both eyes brown
- No; one eye is blue, the other brown.

Typically dogs have two differently colored eyes when they are heterozygous for a specific allele of the **merle** gene, but it can occur for other reasons. Dogs that have 2 blue eyes are not usually homozygous for the allele; their blue eyes are controlled by other genes.

Handout #3: Evaluating Coat Color

The genes for various colors and patterns are difficult to trace unless the colors are evaluated in a consistent, systematic way. The questions below can help guide the process. These questions extract additional information beyond what the handout **Evaluating Dog Phenotypes** does.

Detailed explanations of the loci involved and how the various pigments and regulators interact are provided in the handout Genes Controlling Coat Color.

Question 1: Does the dog have pure black or brown hairs anywhere in its coat?

This question evaluates two loci: E (extension) and B (brown).

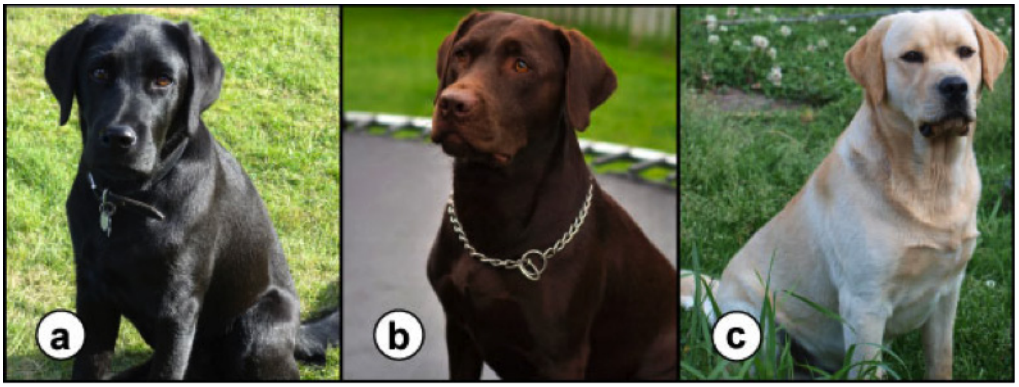
- If a dog has pure black hairs in its coat (#1 below), it is producing the black pigment eumelanin. The dog is either genotype E/E or E/e (simple autosomal dominant)
- If there are no black hairs, but chocolate brown hairs, the dog produces a brown version of eumelanin. That means it is homozygous recessive (bb) for the B locus.
  - The brown color still requires the dog to be either E/E, or E/e, so is an example of epistasis.
- If there are no black or chocolate hairs in the coat, only yellow or red (#2 below), the dog is producing pheomelanin, but not eumelanin. Dogs that are red, yellow, or white (no black) are recessive (ee) at the E locus.

Caution: the black or brown pigment does not have to be in the entire length of the hair. The agouti locus (see Qu. 4-6 below) turns eumelanin deposition alternately on then off as the hair grows. In some dogs, only the tips or only the base of hairs will be black,. In both cases, the animal still is producing eumelanin, so must be E/- (E/E or E/e), and B/- (B/B or B/b).

Question 2: Is the dog solid black (a) or brown (b), or does it have other colors in its coat (c)?

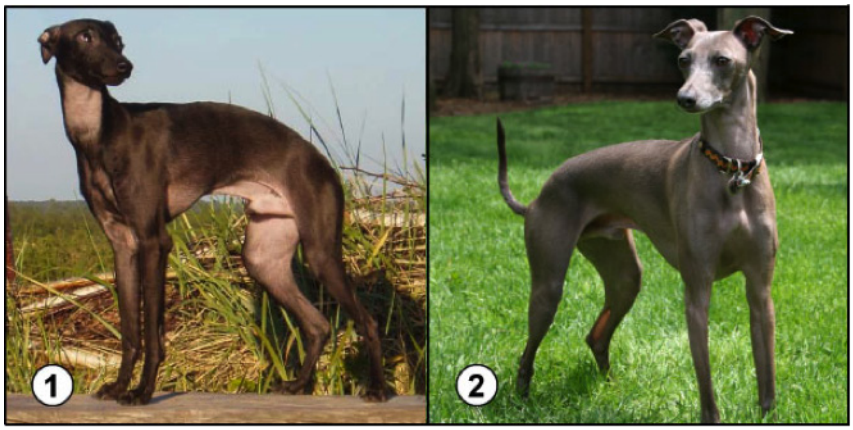
This determines activity of the K (black) locus.

- Dogs with patterned coats or agouti hairs must be recessive (k/k) for this locus. The simplest way to picture this locus is to imagine an autosomal dominant gene that increases eumelanin production and deposition to maximum levels, turning the entire dog black (E/-, B/-, K/-; panel a) or brown (E/-, b/b, K/-; panel b). Dogs that are yellow (panel c) are k/k genotype usually.



Question 3: Is the color dark (#1 below), or does it look faded or bleached out (#2 below)?

This assesses activity at the D (dilute) locus. The D locus is much more obvious when it affects eumelanin. It can be difficult to detect in a dog with e/e genotype.

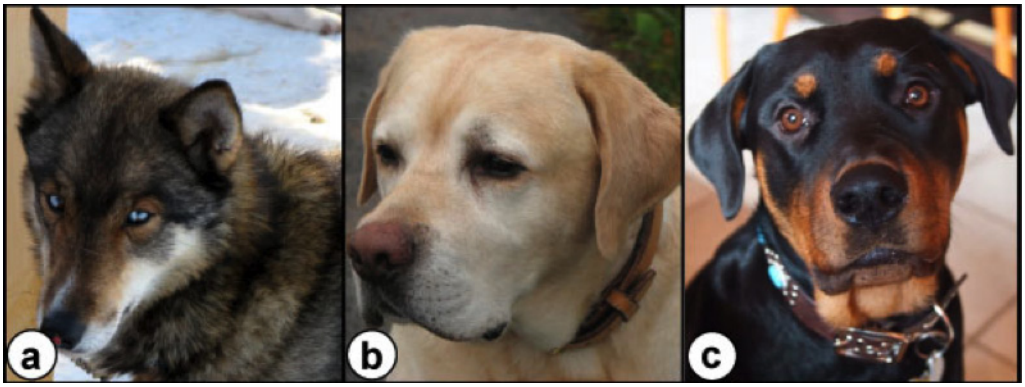


Question 4: Are individual hairs banded with multiple colors (a below)?

Question 5: Is the dog's coat almost completely yellow or red (b below)?

Question 6: Is there an obvious black-over-tan pattern (c below)?

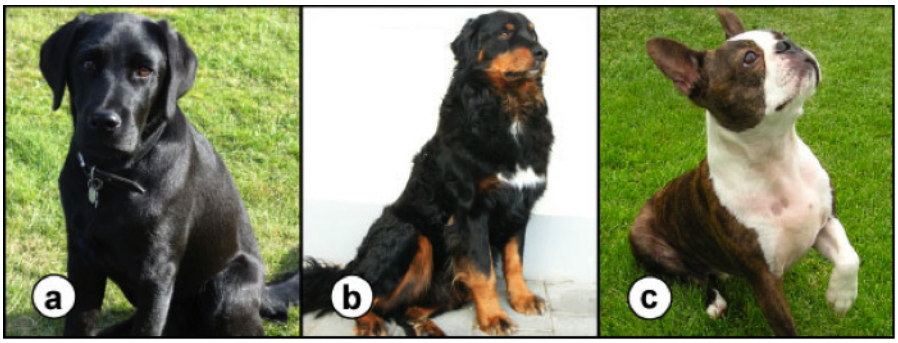
These three questions assess expression of various alleles of the A (agouti) locus.



Question 7: Is the dog solid colored (a below) or does it have white in its coat (b and c below)?

Question 8: Is the white only found on the feet, tail tip, or as a chest star (b below), or does the white area include parts of the legs, chest, head, belly, and back (c below)?

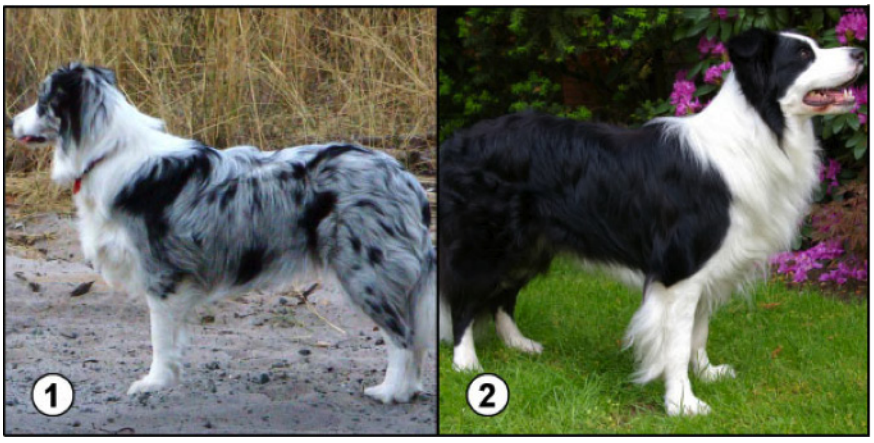
Answers to these questions determine the relative activity of the S (spotting) locus.



Question 9: Does the dog have random, uneven mottled coloration of its coat (#1 below)?

Question 10: Is one eye a different color than the other?

These last two questions evaluate patterns associated with the M (merle) locus.



Handout #4: Genes Controlling Morphology and Coat Structure

Overall Size

Of all animals, dogs have the greatest extremes in body size within one species. The Irish wolfhound (left) and chihuahua mix (right) in the photo below show this extreme range in size. Putting aside anatomic challenges, the two breeds can (in theory) reproduce successfully, because genetically they still are compatible.

Sutter (2007) showed that for most small breeds, size is controlled by the **insulin-like growth factor–1 (IGF-1)** gene, located on CFA 15. An autosomal recessive allele for IGF-1 is found in 9 small breeds and is nearly absent from 30 large breeds. The autosomal recessive allele is due to a single 1 bp SNP (single nucleotide polymorphism) in Exon 3 of IGF-1.

Some dogs are small because they have a recessive allele for a gene that codes a protein through which IGF-1 acts. For example, an autosomal recessive allele of the IGF-1 receptor (on CFA 3) is responsible for the small size of dachshunds and Brittany spaniels.

Breeds that are small because of a recessive allele for IGF-1 or IGF-1 receptor		**Breeds lacking the IGF-1 & IGF-1 receptor alleles linked to small size**
• Airedale terrier • Australian cattle dog • Basenji • Beagle • Bichon frise • Boston terrier • Brittany • Bull terrier • Cairn terrier • Chihuahua • Chinese crested • Cocker spaniel • Dachshund • French bulldog • Italian greyhound	• Jack Russell terrier • Lhasa apso • Maltese • Papillon • Pekingese • Pomeranian • Poodle (mini & toy) • Pug • Schnauzer (mini) • Scottish terrier • Shetland sheepdog • Shih tzu • Welsh corgi • Whippet • Yorkshire terrier	• Akita • Bernese mountain dog • Bullmastiff • Great Dane • Great Pyrenees • Irish wolfhound • Mastiff • Saint Bernard • Schnauzer (giant)

Leg Length

In dogs short legs relative to body size is a form of achondrodysplasia. An **FGF-4 retrogene** located on CFA 18 is the source of the autosomal dominant allele. It causes characteristic short-limb phenotypes. Long legged dogs and large breeds cannot be silent carriers; if the allele is present, a dog has short legs. To learn how this defect arose originally, read Parker (2009.)

This basset hound's front legs are much shorter than the overall length of its body. The same allele causes a type of human dwarfism.

These breeds have short legs due to this allele	**These breeds are so small their legs do not look short relative to body size. However, they still have the FGF-4 allele.**	**These short-legged breeds do not have the FGF-4 dysplastic allele. Why they have short legs is not known**
• Basset hound • Cairn terrier • Corgi • Daschshunds • Pekingese • Scottish terrier • Shih tzu • Swedish valhund • West highland terrier	• Japanese chin • Chihuahua • Yorkshire terrier	• Pug • Cocker spaniel

The allele is fixed in these pure breed dogs, so any puppy that has one of these dogs as a parent will have short legs.

Coat Structure

Three genes determine the length and texture of a dog's coat: **FGF-5 (L locus), R-spondin 2 (W locus),** and **keratin-71 (R locus)**. Together they produce seven different coat phenotypes (List reprinted from Cadieu, 2009):

- Short plain hair (e.g. Basset Hound)
- Short wiry hair (e.g. Australian Terrier)
- Curly and wiry hair (e.g. Airedale Terrier)
- Long hair (e.g. Golden Retriever)
- Long with furnishings (e.g. Bearded Collie)
- Long and curly (e.g. Irish Water Spaniel)
- Long and curly with furnishings (e.g. Bichon Frisé)

Coat length (L locus) is determined by the FGF-5 gene on CFA 32. This same gene controls hair length and growth in many mammalian species, including humans. A short coat is the wild type phenotype. A single nucleotide change from G to T converts Cys-95 to Phe in Exon 1 of FGF-5, which stimulates longer hair. The "G to T" allele is autosomal recessive, so short-haired dogs can be either L/L or L/l genotype. Long haired dogs are l/l genotype.

In ~30% of breeds, L/l genotype produces medium length hair, suggesting the underlying mutation may be partly penetrant. When in doubt, keep it simple: only dogs with l/l genotype will have long hair.

A German shepherd/spitz mix. It has much longer hair (look at the length around the shoulders, neck, face, and tail) compared to a bulldog, black Labrador, or greyhound, so is recessive (l/l) genotype.

Curly coat (R locus) is also the result of an autosomal recessive mutation. Wild-type dogs have straight hair. Curly-coated dogs are homozygous for a 1 bp change (C to T) in Exon 2 of KRT71, the gene coding for keratin 71, on CFA 27. This **single nucleotide polymorphism** changes Arg-151 to Trp. As a result their hair does not grow straight, but curls instead. Curly coated breeds (like poodles) are genotype r/r, while flat coated breeds (like Labrador retrievers) are genotype R/R.

Bichon-type breeds occur in both curly-haired and straight-haired forms.

1. Havanese is a straight-haired Bichon breed. This dog likely is homozygous for the wild type allele (R/R) because they are true-breeding.
2. Bichon Frisé, a curly haired breed. This dog must be homozygous recessive (r/r).

Wiry coat with furnishings is controlled by the **W locus**. A wiry coat and long facial hair such as moustaches or eyebrows ("furnishings") is caused by an autosomal dominant allele of RSPO2, the R-spondin 2 protein, on CFA 12. An insert in the 3' UTR increases RSPO2 gene expression 3-fold. The dominant allele is indicated by W, recessive by w. A puppy needs to inherit only one copy of the W allele to have a wiry coat and facial furnishings.

A miniature schnauzer with bushy eyebrows and a long mustache. This dog has not been trimmed recently, so we can see the characteristic long wiry hair of the breed. Schnauzers are true-breeding, so the allele is fixed as (W/W). However, a single copy of the allele (W/-) is enough to produce the phenotype.

Hairlessness is controlled by the **F locus**. The F locus is the FOXI3 gene on CFA 17. The exact function of FOXI3 is unknown, but other proteins in the FOX family control embryonic development in mammals. The equivalent gene in mice regulates development of teeth and fur cells. The hairless allele is a 7 bp duplication in Exon 1 of the FOXI3 gene. The allele is inherited as an autosomal semi-dominant. Heterozygotes are hairless, but dogs homozygous for the mutation die as embryos.

Dog hairlessness is a recent mutation that arose about 4,000 years ago in Mexican hairless dogs. The mutation was intentionally introduced to the other two breeds by mating them with Mexican hairless dogs. As a result Mexican hairless, Peruvian hairless and Chinese crested dog breeds all have the same mutation.

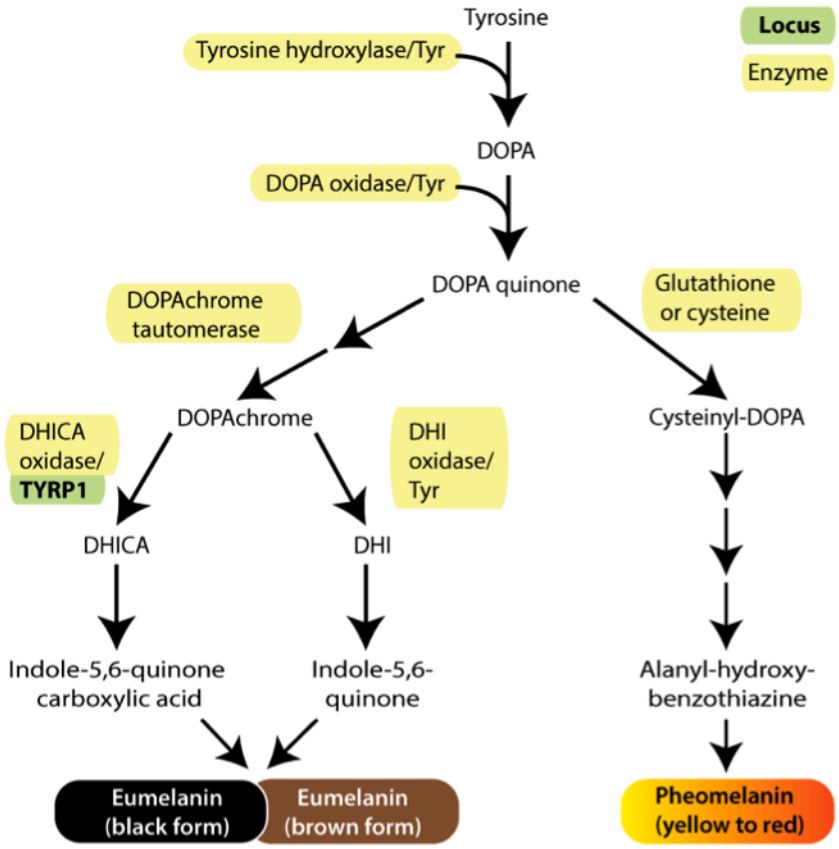
A Mexican hairless dog (a heterozygote, F/f), also called a Xoloitzcuintlis (Xolo for short), and a short-haired littermate (homozygous recessive f/f). Xolos have been present in Mexico for 3000 years. They are a well-documented historical example of how founder mutations ultimately become defined breeds.

Handout #5: Genes Controlling Coat Colors

Coat color is the most challenging physical feature to assess in dogs, because several loci interact to create the phenotypes. It helps if you know how the two pigments in a dog's coat are produced. After that, you can think about genotypes and phenotypes in terms of actual protein activities.

The Biochemical Pathways

Relative levels of two pigments determine a dog's coat color: **eumelanin**, which can be either brown or black, and **pheomelanin**, which is yellow to orange-red. Both pigments are generated by metabolism of tyrosine. A schematic diagram of the pathway is below.



In melanocytes, the default action is to produce yellow-red pheomelanin. Eumelanins are only made when melanocytes receive specific signals from the **melanocortin receptor (MC1R; the E locus)**. MC1R has two main ligands: melanocyte stimulating hormone (α-MSH) and agouti signaling peptide (**ASIP**, which is the product of the gene at the **A locus**).

ASIP and α-MSH compete to bind to the receptor. When ASIP binds, melanocytes produce pheomelanin primarily; when α-MSH binds, eumelanin is produced. Animals with agouti coats have **individual hairs** with alternating bands of black or brown and yellow/red, corresponding to alternating binding of the two ligands.

Different alleles of the A locus determine how strongly ASIP binds. Different alleles for the E locus determine how MC1R signals in response to each ligand.

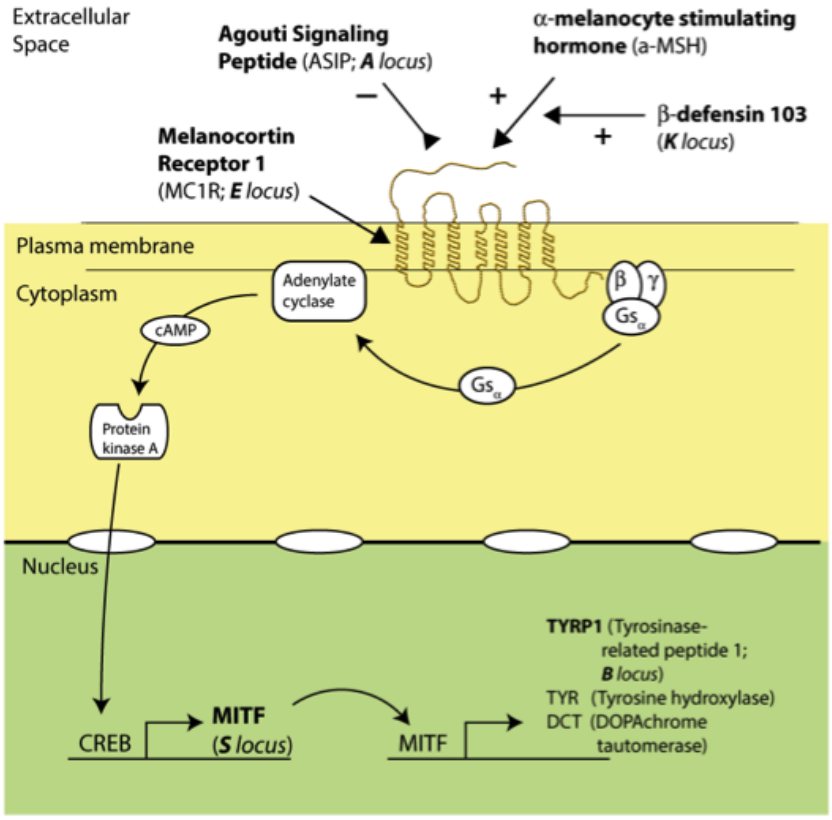
Two other loci affect coat color. **β-defensin (K locus)** is a co-activator that binds to MC1R and prevents ASIP from binding. This locus is responsible for some pure black dogs. The micropthalmia transcription factor (**MITF; the S locus**) controls developmental programs before birth, then after birth, it controls expression of the enzymes needed to make melanin. One of the enzymes, tyrosinase, is required for BOTH pheomelanin and eumelanin production. Mutations that block MITF prevent either color from being produced, and the animal's coat is white.

Seven Loci Determine Coat Color & Pattern

Four loci (E, B, K, and A) control the relative levels and types of melanins made. Three loci (D, S, and M) control distribution of the melanins.

The **Extension or E locus** on CFA 5 codes for MC1R, which is the protein that controls whether or not melanocytes can respond to melanocyte stimulating hormone (MSH), and how much eumelanin they make. There are 3 alleles for the E locus:

- **E** codes for normal receptor activity. Animals will produce black eumelanin. This is the dominant allele.
- $\mathbf{E}^{M}$ codes for a mask of extra eumelanin. Animals have a black mask on their nose and face, but a lighter color on the rest of their body.
- **e** codes for a defective version of the MC1R. Dogs that are homozygous recessive e/e cannot respond to MSH, so cannot make eumelanin at all. Their coat can only be yellow-orange (from pheomelanin) or white.



Schematic showing how MC1R regulates melanin synthesis.

Colors associated with the E locus.

1. A Karelian bear dog's coat has fully black hairs due to the E allele.
2. The black muzzle and eye-band on this gray German shepherd dog are due to the E^M allele.
3. Two Labrador retrievers that are homozygous recessive (e/e.) They show the range in color that is possible for dogs that have only pheomelanin, from pale yellow (others can be nearly blonde) to orange-red.

The **Brown (B)** locus on CFA 11 codes for tyrosinase-related protein 1 (TRP1 or TYRP1). There are four alleles for this locus:

- **B** is wild type and dominant. It allows the normal production of black eumelanin.
- **b** is recessive. Without TRP1, the last step in eumelanin synthesis does not occur. The final pigment is milk chocolate brown rather than black. Chocolate Labrador retrievers show this color.

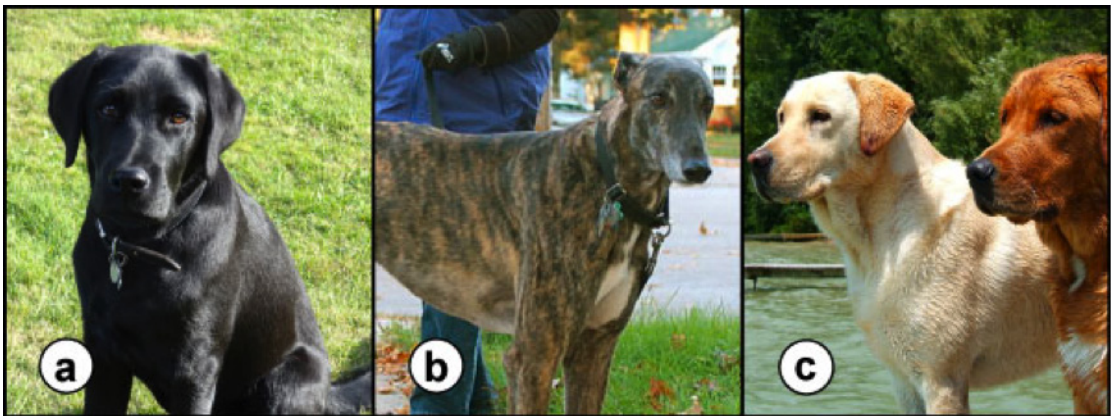
The difference in black (genotype B/B or B/b, left) and brown (b/b, right) coat color phenotypes.

The **Black (K)** locus is responsible for most all-black dog breeds. There are 3 alleles for this locus. They form an allele series; each is dominant to the allele below it in the series:

- $\mathbf{K}^B$ or $\mathbf{K}^{Black}$ is a dominant allele. Dog is solid black or brown. One copy of this allele is sufficient for a dog to be completely black.
- $\mathbf{k}^{Br}$ is recessive to K^B, but dominant to k^y. Animals will have a mix of solid and agouti colored areas, known as brindle coloring.
- $\mathbf{k}^y$ is recessive. Dogs that are homozygous for this allele will display whatever pattern the A (agouti) locus is coding for.

The K locus is on CFA16. The gene codes for beta-defensin 103. CBD103 is an immune modulator, but also controls coat color by binding to MC1R and increasing receptor activity. The dominant allele causes an animal to be a single solid color; it will be black or brown, depending on the alleles for the B locus.

The K locus cannot produce a black dog unless there is at least one "E" allele for the E locus. A dog that is "e/e" does not produce eumelanin, so will be yellow or red regardless of the alleles at K or B.



The coloration associated with alleles at the K locus.

A. Black Labrador retrievers have K^B/- genotype; the second allele may be any of the 3 alleles for the K locus.

B. Greyhound showing the brindle pattern (alternating areas of single and agouti colored hairs.) This dog will be either k^{Br}/k^{Br}, or k^{Br}/k^y.

C. Two yellow Labrador retrievers, genotype k^y/k^y.

The **Agouti (A) locus** on CFA 24 is unusual in that no allele at this locus is truly dominant. All of the alleles will be hidden by the K^B or k^{Br} allele. A dog must be k^y/k^y for any of the "a" alleles to be visible.

The agouti signaling peptide (ASIP) competes with α-MSH to bind to MC1R. This results in alternating bands of dark black or brown eumelanin and yellow to red pheomelanin in individual hairs. Agouti hair patterns require both types of melanin; a dog that has an e/e genotype does not produce eumelanin, so it cannot show agouti coloration. However, the dog can be a carrier or even homozygous for one of the "a" alleles.

There are four alleles for the A locus:

- **a^y** codes for very high levels of ASIP. Animals are pale yellow to fawn-colored, but can have a few scattered black hairs in their coat.
- **a^w** is the ancestral allele. It is widespread in wolves but rare in modern dog breeds. German shepherds are one of the few breeds where this allele still can be found. German shepherds carrying this allele are much darker on the legs, chest, and face, and look more like wolves. They will not have the black and tan pattern we usually associate with German shepherds.
- **a^t** codes for "black and tan" pattern. Dogs carrying this allele have black or very dark heads, backs and tails, with tan, yellow, red, or brown legs, bellies, and chests.
- **a** is the true recessive. Dogs that are a/a homozygous cannot produce pheomelanin, so are solid black. This genotype is identical to that of the dominant black locus, but is inherited as an autosomal recessive.

The **Dilution (D)** locus on CFA 25 codes for MLPH (melanophilin). This recessive mutation does not affect total melanin production, but makes the pigment clump inside hair cells rather than spread evenly. As a result the coat looks faded or diluted. This allele affects both types of melanin, but is most obvious when it affects black eumelanin; the result is a slate-blue or gray coat.

- **D** is the allele for normal melanin dispersion.
- **d** is the recessive allele that prevents dispersion.

Dogs that are genotype D/D or D/d have dark coats. Dogs must be homozygous recessive (d/d) to show the diluted color phenotype.

Different patterns produced by A alleles.

1. Fawn colored Great Dane puppy. Like most fawn colored dogs, she has few black hairs overall. They are concentrated on her face in a melanistic mask due to the E^M allele.
2. Bred to resemble wolves, tamaskans are a recently created breed developed from German shepherds. The distinctive mixed agouti patterns are especially clear on the dog in the back. Very likely these dogs are a^w/a^w genotype.

3-5. Large (3), mid-size (4) and small (5) dogs with the black and tan pattern associated with the a^t/a^t genotype for the agouti locus.

1. This slate blue pit bull (1) is homozygous recessive (d/d). If it was genotype D/D or D/d it would be entirely black.
2. It can be hard to tell if a brown dog (2) is homozygous d/d. This mixed breed appears to be diluted phenotype, but its coat may simply be within the normal range of brown color. Brown/dilute dogs that are paler brown are more obvious.

White hair in a dog's coat means BOTH melanins are missing. To produce a white coat, the responsible alleles must prevent ALL melanin production. Evaluating white is the most challenging of all colors, because at least two different genetic pathways and one non-genetic mechanism can produce white dogs.

Genetic Path 1: The **S locus** on CFA 20 codes for **MITF (micropthalmia associated transcription factor)**, which controls development and migration of melanocytes. This transcription factor ALSO controls MC1R expression. Inactivation of MITF eliminates pigment to create a partially or completely white coat. There are at least 2 alleles for MITF: wild type (S), and an alternate allele in which the gene has been inactivated by a SINE (short interspersed nuclear element) insertion (s). In many breeds, S and s are a simple dominant/recessive pair. A dog with genotype S/S or S/s will have little or no white in its coat, while a dog that is homozygous recessive (s/s) will have a large patch of white on its belly. How far the white extends up its sides, shoulders, and chest will vary. Some s/s dogs have white only on their legs chest, and belly (mantle pattern). Other s/s dogs have white extending up their shoulders and around their neck (Irish spotting pattern). Still others are mostly which with randomly spotted colors (piebald) or nearly entirely white. In a few breeds, S and s appear to be co-dominant, so that S/S dogs are fully colored, S/s dogs are mantled or Irish spotted, and s/s dogs are nearly white.

Genetic Path 2: There is one study that concluded Samoyeds are white because they are genotype "e/e, a/a." In this case, the "e/e" genotype prevents eumelanin synthesis, and "a/a" genotype prevents pheomelanin synthesis (Bowling, 2010; Schmutz, 2007).

Non-Genetic Path: Dogs **also** develop white spots on their chest ("stars"), toes ("slippers" or "socks"), and tail tip if melanocytes do not migrate into these locations during development. These patches of white are entirely the result of non-genetic developmental variation. Many dogs have them, particularly mixed breeds.

Variation in white phenotype. All of these dogs are s/s (homozygous recessive).

1. Nova Scotia tolling duck retrievers with various sized white patches on their chests. As this group shows, white phenotypes can vary a lot. The front two dogs have patches large enough to suggest they are mantle pattern, not just white chest stars.
2. A border collie. The pattern of a white collar around his neck that continues down his front legs and along his belly is called Irish spotting.
3. A piebald Brittany spaniel. Piebald dogs have unevenly shaped color spots on a mostly white background.
4. Dogo Argentinos are nearly pure white, but will have occasional color patches on the chest or an ear. White boxers and bull terriers have similar color.

The **Merle (M)** locus on CFA 10 codes for two integral membrane proteins, PMEL17 and GP100, that regulate melanocyte formation in eyes and skin. Merle pattern is a solid base color (usually red/brown or black) with uneven lighter blue/gray or reddish mottled patches. Dogs often have eyes that are pale, unevenly colored or mismatched. This allele is an autosomal dominant mutation. It interferes with pigment cell development, so dogs that are homozygous for this allele may be blind, deaf, or both. M codes for spotty (merle) melanin dispersion. Although m is recessive, it is also wild type, so it is the major allele in most breeds.

1. An Australian shepherd. Mismatched, patchy coloring and a mix of slate, black, brown, and white indicate it is heterozygous M/m. The white collar, chest, throat, and forelegs are determined by the S locus. This pattern of white indicates the dog is probably homozygous s/s.
2. A merle border collie. Heterozygous M/m dogs often have mismatched eyes. In contrast, M/M dogs often are nearly white, and usually blind and/or deaf.

Sample Problem 1: Low Difficulty

A recent news report told the story of a determined male basset hound who seemed to be particularly attracted to Labrador retrievers, despite the obvious height challenge. The photos below show the basset hound and his latest mate.

The Parents

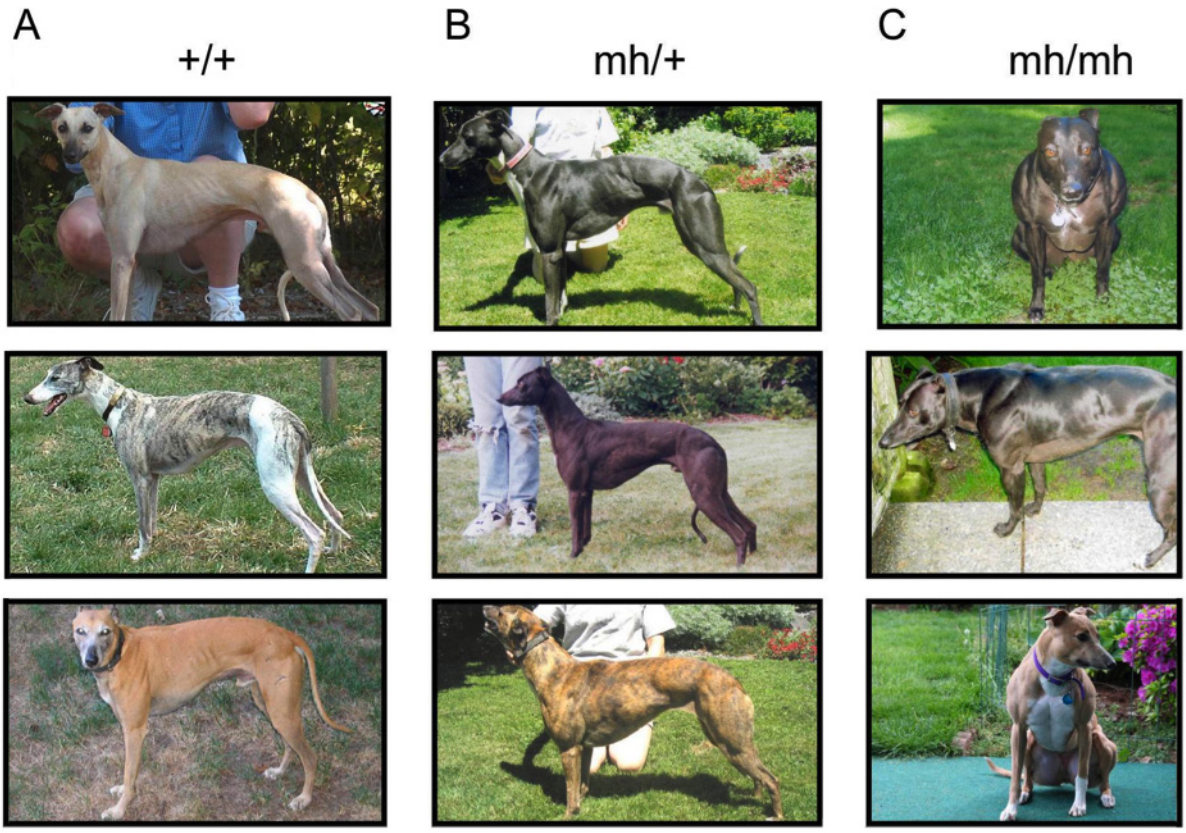
Questions:

1. Which of the 4 pups pictured is most likely to be one of their offspring?
2. Using a Punnett square, explain your rationale.

Sample Problem 2: Intermediate Difficulty

Whippets are small, agile, very fast dogs that were bred to run down rabbits and other game. It is not unusual for a whippet to run 25-30 mph. Today some fanciers race them. Breeders select and mate the fastest whippets in hopes of producing puppies that also are champion racers. Unfortunately, a recent study found that the fastest whippets may be heterozygous for a mutation in the myostatin (MSTN) gene. Heterozygous whippets (mh/+) are stronger, but still lean and graceful. Homozygous recessive dogs (mh/mh), called "bully whippets," develop huge muscles that prevent them from running fast.

The photos below show 3 normal (+/+) dogs, 3 heterozygotes (mh/+), and 3 "bully whippets" (mh/mh).



Questions:

To avoid diluting the gene pool, breeders will not intentionally cross a bully whippet with a normal-appearing dog. Even so, it is estimated that 20% of all champion racers are heterozygous (mh/+) for the myostatin defect.

Suppose a breeder selects 2 champion racers at random, and mates them. When the mother gives birth to a litter of puppies:

1. What is the probability that one of the puppies will be a "bully whippet"?
2. What is the probability that two of the puppies will be "bullies"?

When the pups from this first pairing reach 1 year of age, one female (named Wendy) from the litter turns out to be a bully whippet. Soon after that the breeder selects a different champion male racer at random, and breeds him with Wendy's **mother**.

3. When the original mother has puppies with this new male, what is the probability that one of the puppies in her second litter will be a bully whippet?
4. Against the advice of his friends, the breeder decides to mate Wendy the bully female. He picks yet another champion male at random. What is the probability that one puppy from a normal-appearing male racer and a bully female whippet will ALSO be a bully?

Sample Problem 3: High Difficulty

If two female dogs have pups around the same age, they sometimes will adopt each others' pups. This is not a problem, except when the breeder needs to be CERTAIN which pups were produced by which mother. The photo below was taken by a Labrador retriever breeder who had two different champion female dogs that both whelped their puppies the same night.

1. Could all these pups belong to one mother, or was the yellow one adopted from a different litter? Using a Punnett square, explain your rationale.
2. If these puppies are siblings, what did their parents look like?

Sample Problem 4: Stacked Series

Low Difficulty

1. Using your Evaluation Guides, what are the observable phenotypes for this dog?
2. Neither of the parents of this particular dog had long hair. Using a Punnett square, show how they could have produced this phenotype.

Intermediate Difficulty

3. This dog came from a litter with 8 siblings. One sibling has short hair and is almost entirely black. What are the genotypes of the parents? Given those parents, would it be possible for one of the other siblings to be short haired but yellow? Show how you arrived at these answers.

High Difficulty

4. Type 1 rod-cone dysplasia is due to a defect in cGMP-specific phosphodiesterase 6B. The affected gene is on Chromosome 3, which also is where the IGFR-1 locus is located.

   A. Based on chromosomal maps, how far apart are the two loci?

   B. This dog is a carrier for Type 1 rod-cone dysplasia. Given the distance between the two loci, what is the probability that the mutant IGFR-1 will separate from PPE6B in this dog's offspring?

Notes for the Instructor

Accessing the TGWD Resources Catalog

The URL for Teaching Genetics With Dogs is:
http://www.adapaproject.org/doggenetics/.
Non-registered visitors, instructors, and students can access news stories, guides, handouts, and reference data tables. Answer keys for the four example problems included in the Student Outline are available online (in addition to Appendix A.) We encourage visitors and users to tell us what they find useful, what needs revision or improvement, and what resources they would like to see added.

Access to answer keys for all other word problems is restricted to registered users who have been approved by the project administrator. To request access, go to the project home page, and look for **Contact Us** in the side panel. Alternatively use the online request form at: **https://www.adapaproject.org/doggenetics/tiki-index.php?page=Contact Us**

Strategies for Using TGWD Resources

Many TGWD resources and examples can be exchanged 1:1 for in-class examples and problem sets in an existing genetics course. However, we suggest taking time to review the course structure, and incorporating active learning activities where appropriate that let students explore genetics questions in a more open-ended way.

Two basic active learning exercises that use canine genetics are provided in the next section. They are designed to reinforce basic genetic principles as well as stimulate higher level thinking. Interspersing these activities in a highly structured course such as genetics gives students a conceptual context for the facts they learn.

Expanded versions of these sample exercises, and links to additional resources at other institutions, are available on the main project web site. From the home page, go to **Resource Catalog**, then near the bottom look for **FAQs and Additional Resources**.

Sample Exercise 1: How Did Wolves Become Dogs? Introducing Students to Canine Genetics

Estimated time:

40 minutes

Goals of the Exercise:

- Increase students' comfort with active learning.
- Introduce question-oriented thinking.
- Introduce students to dogs as genetic models.
- Reinforce these concepts, principles: roles of genes in anatomy, physiology, and behavior; genetic variation.

Preparation:

Have 3-4 photos ready to show in succession: a mature wolf, a size comparison of an Irish wolfhound or Great Dane and chihuahua (or other extreme sizes), and a purebred Chinese crested dog or bulldog. Photos are available in the Images Gallery on the TGWD website.

Introduction and Challenge:

1. From genetic data we know that dogs are domesticated descendants of wolves. (Show photos of mature wolf)
2. Most wolves look fairly similar, and have similar sizes. Now look at how much difference in size there is in dogs. (Show size difference of Irish wolfhound or Great Dane and Chihuahua)
3. Size is not the only change though. Look at the other changes in dogs versus wolves. (Show wolf again, then the purebred Chinese crested dog or bulldog.)
4. So how did we get from wolves to dogs? What had to change?

Think-Pair-Share Activity

1. Working with a partner, think about all the different dogs you know. How are dogs different from wolves?
2. Working with your partner, decide which ones are controlled by genetics, and which are not.

Group Discussion

Ask students to list the differences they identified. Let each pair give 1-2 examples, then ask another group, so no one dominates the discussion. Assemble a list from the entire class for Question 1 before asking for their responses to Question 2.

Resources Used and Notes

We used this exercise at the 2013 ABLE Meeting to introduce the project to workshop participants. The first question is a warm-up to find out what students know already. The second question sets up a false lead; typically all differences they identify are genetic. A better question would be, "which differences are simple genetic traits, and which differences have complex genetics?"

Powerpoint slides for this activity are available in the Resources Catalog. Additional open-sourced photos are available from the Project Photo Gallery.

For a more difficult version of this activity, have students evaluate evidence for the origin of dogs. Look at Nature's SciTable tutorial (**http://www.nature.com/scitable/topicpage/genetics-of-dog-breeding-434**) for a dataset.

Sample Exercise 2: Hybrids Galore-Labradoodles and Lurchers

Estimated time:

1-2 hours

Goal of the Exercise:

- Train students to evaluate phenotypes systematically.
- Show students how to deduce dominant and recessive inheritance patterns from direct observation.
- Reinforce these concepts or principles from lecture: genotype versus phenotype, simple dominant versus recessive inheritance.

Preparation:

Select 1-2 photos of designer dogs for each pair of students. Be sure to include the names of the two breeds that are the parents of the hybrid. If this exercise is done in class, students will need access to the web for online searching.

Introduction and Challenge:

There have been recognized pure-breed dogs for nearly 300 years. Each breed is a closed, reproductively isolated population, and fanciers work to maintain a certain look or set of features, called the "breed standard." More recently, some breeders have been creating "designer dogs." They are not random mutts. They are hybrids, produced when two known parents from different breeds are crossed intentionally. For example, in the British Isles farmers create **lurchers** by crossing an Afghan hound or Saluki with a collie or large terrier. The lurcher has a mix of features from the parents that benefit the farmer. A more recent designer dog is the **Labradoodle**, a companion dog creating by crossing a Labrador retriever with a poodle.

By studying designer dogs we can make and test hypotheses about how certain physical traits are inherited. Your instructor will give you 1-2 photos of designer dogs, with the names of the two breeds that were crossed to produce it.

Activity

1. Tell students to use the **Guide to Evaluating Body and Coat Structure Phenotypes** to make a list of the specific observable physical traits that their designer dog has.
2. Next, they should search online for 1-2 photos of each of the two breeds that are its parents. Again, they can use the **Evaluation Guide** to determine specific traits.
3. They should catalog which traits are found in:
    - One parent breed and the designer dog offspring, but not the other parent?
    - One parent breed but not in the designer dog?
    - Both parent breeds but not in the designer dog?
    - Neither parent but only in the designer dog?
4. Based on their observations from Question 3, they should hypothesize which traits have:
    - Simple dominant inheritance?
    - Simple recessive inheritance?

Group Discussion

Ask students to summarize the phenotypes of their hybrid and parents, preferably as a short presentation. If time is short, it can be a homework assignment.

Resources Used and Notes:

The Wikimedia Commons page on hybrid/designer dogs is a good starting point for photographs (**http://commons.wikimedia.org/wiki/Category:Dog_hybrid**.) A Google search for "designer dog" will produce hundreds of breed pairs as well. Using the **Guide to Evaluating Body and Coat Structure Phenotypes** will not uncover every possible trait, but will provide students with several traits to evaluate.

To complete this exercise students must think deeply about genetics questions, rather than work towards one correct answer. Any two breeds can (in theory) be combined to produce a designer dog; if you cannot find photos of a particular breed pair, try searching mixed breed dogs instead.

To extend the basic exercise have students return at a later date, and see if they correctly identified which traits are dominant versus recessive. Alternatively they can use the genotype guides in the TGWD Resource Catalog to check their predictions.

To make the exercise even more challenging, ask students to pick one of their designer dog's parent breeds, then switch partners. Using just their own data, have them predict the phenotypes of the designer dogs that would be produced if they "mated" with their new partner.

Adding New Resources

Teaching Genetics With Dogs is an educational resource site produced and managed by ***The Adapa Project***, an open consortium of educators, students, & others at Wake Forest University who want to help ALL students learn science successfully. Our goal is to build a collection of word problems, reference materials, links to news stories, tutorials, etc., that spans all of the topics taught in typical undergraduate genetics courses. Our working list of topics is in Appendix B. We encourage instructors who teach general introductory genetics courses to review our working list and tell us if any core concepts are missing.

At the ABLE 2013 Annual Meeting, participants in two major workshops designed 22 new cases for this project. As cases are finalized, they will be added to the TGWD Resources Catalog. We invite others who create new resources to add their materials to our project site as well. Contributions count as peer-reviewed, digital scholarly activity. Materials are licensed for non-profit educational use under terms of a Creative Commons CC-BY-NC-SA 3.0 license, and remain the property of their original authors. All contributed documents, text, and media files are tagged with their original sources and attribution data before release.

Acknowledgments

We want to thank the participants in the two major workshops at the 2013 ABLE Annual Meeting in Calgary for sharing more than 20 ideas, draft problems, and completed problems to be added to the project, and especially for their insights into specific challenges their students face as they learn genetic principles.

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About the Authors

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Appendix A

Answer Keys for Sample Problems

Sample Problem 1

This problem is designed to train students to work through key characters methodically. If students use the list of questions in the Evaluation Guide, they will find total size and head shape are not informative. Ear length might be useful but is polygenic, so also is not a strong phenotype to use. Similarly, both parents have short, flat coats with straight hair and no furnishings, and long tails. A short flat coat eliminates the wiry-haired pup, but none of the others. Leg length relative to body length is the only useful feature (without going to coat color).

Leg length is short for the basset hound, and long for the retriever. Legs that are significantly shorter than total torso length are due to an autosomal dominant mutation, L (the same mutation causes one form of human dwarfism). Basset hounds are a pure breed that always produces short-legged offspring. Therefore it is safe to assume the allele for short legs is fixed and that all basset hounds have genotype L/L. The retriever has long legs so must be genotype l/l. Given the parents, their puppies can be:

		Male Basset	
		L	L
Female Labrador	l	L/l	L/l
	l	L/l	L/l

Only short legged heterozygous puppies can be produced in the first generation. So of the 4 choices, Pup #2 is the only one that can be their offspring, because it is the only dog with shortened legs.

Type of inheritance and genetics principles demonstrated

- Punnett Square method
- Monohybrid cross of simple autosomal trait

Comments and Variations

A variation that makes the problem more difficult is to not tell students short legs is a fixed trait. This means the basset male could be L/L, or L/l, and make two different crosses possible.

		Male Basset	
		L	L
Female Labrador	l	L/l	L/l
	l	L/l	L/l

OR

		Male Basset	
		L	l
Female Labrador	l	L/l	l/l
	l	L/l	l/l

In this scenario, according to Mendelian inheritance alone, these parents could have produced three of the puppies. Only the wiry-haired pup is eliminated.

Potentially Difficult Concepts

Students often struggle when there is no clear answer. Problems such as this can help students become more comfortable with ambiguity. However, it is important they know in advance that the answer to a question might be “we cannot know.”

Sample Problem 2

1. Given the probability that any given parent is genotype M/m = 0.20, the probabilities for 2 adults of this genotype mating is 0.20 x 0.20. From this cross, the probability of a bully whippet (i.e., m/m homozygous recessive genotype) is 1 in 4 (0.25). Thus the overall probability of a single bully offspring is:

$$0.20 \times 0.20 \times 0.25 = 0.01, \text{ or } 1\%.$$

2. The birth of each bully puppy is an independent event. Therefore, the probability that two would occur in a single mating is:

$$(0.01 \times 0.01) = 0.0001, \text{ or } 0.01\%$$

3. Now we know the genotype of the original female parent. She must be M/m because she produced a bully puppy, so p(M/m) = 1.0. The probability that the other randomly chosen parent is genotype M/m remains 0.2. Thus the overall probability of another bully offspring is:

$$0.2 \times 1.0 \times 0.25 = 0.050, \text{ or } 5\%$$

4. Again we know the genotype of Wendy, the female parent. She must be m/m (p=1.0). The probability that the other randomly chosen parent is genotype M/m remains 0.2. This time, mating would be m/m (female) x M/m (male), which has a 50% probability of producing a bully whippet. Thus the overall probability of another bully offspring is:

$$1.0 \times 0.2 \times 0.5 = 0.10, \text{ or } 10\%$$

Type of Inheritance and Genetics Principles Demonstrated

- Monohybrid cross with 1 autosomal trait that is present at low allele frequency.
- Probability method
- Rule of multiplication

Comments and Variations

This problem is designed to train students to work with probabilities. The purpose of questions 1 and 2 are to evaluate students' understanding of probability. The number of puppies born in each litter is a distractor; in this scenario it is irrelevant. Question 3 shows whether students understand that probability changes once the phenotype of the offspring is known.

Potentially Difficult Concepts

A potential point of confusion in Qu. #1 is that we only have the probability that any two dogs are heterozygotes. By itself, this is not enough information to calculate the allele frequencies. However, most breeders avoid crossing a known bully whippet. So it is safe to assume that 80% of the racers are M/M, and 20% are M/m, and that we can ignore the fraction of the population that is m/m.

For subsequent questions, the original probabilities in the first generation no longer apply. Students must define a new probability for the mother in questions #3 and #4. This can be a sticking point for students if they do not understand that the two are independent events.

Sample Problem 3

1. First students should decide possible genotypes. Three loci (E, K, and A) interact to determine whether a dog is black. A dog can appear entirely black due to either the K or A locus. Given that most of the puppies are black, we will assume a dominant allele (i.e., the K locus) is more likely to be controlling black color. It is POSSIBLE that the puppies are black because they are genotype a/a, but less likely because all but one puppy would need to be homozygous recessive. Therefore:

    - E locus - black dogs must produce eumelanin, so they must be either E/E or E/e.
    - K locus - black puppies can be K^B/K^B, K^B/K^{Br} or K^B/k^y.
    - A locus - the A locus would be masked by K^B. We cannot characterize the A alleles for certain.

For the yellow puppy:

- E locus - must be homozygous recessive (e/e) to be yellow.
- K locus - uncertain.
- A locus - uncertain.

The e/e genotype is sufficient to produce yellow coat, which is why the genotypes for K and A are not known for certain.

The observed F1 genotypes are:

Yellow pup: e/e; K?/K?; a?/a?

Black pups: E/-; K^B/K?; a?/a?

Working backwards, two all black parents could produce these pups if both were heterozygous at the E and K loci:

One parent - E/e; K^B/K?

Other parent - E/e; K^B/K?

If we set up the Punnett square:

	E-K^B-	e-K^B-	E-K?-	e-K?-
E-K^B-	E/E K^B/K^B	E/e K^B/K^B	E/E K^B/K?	E/e K^B/K?
e-K^B-	E/e K^B/K^B	e/e K^B/K^B	E/e K^B/K?	e/e K^B/K?
E-K?-	E/E K^B/K?	E/e K^B/K?	E/E K?/K?	e/e K?/K?
e-K?-	E/e K^B/K?	e/e K^B/K?	E/e K?/K?	e/e K?/K?

The phenotypes for the cross are:

	E-K^B-	e-K^B-	E-K?-	e-K?-
E-K^B-	black	black	black	black
e-K^B-	black	black	black	black
E-K?-	black	black	black	yellow
e-K?-	black	black	black	yellow

According to this analysis, it is reasonable to expect an occasional yellow puppy in a litter of black ones. On average, 1 in 8 puppies from these parents would be yellow. This is about the ratio shown in the photo.

Type of Inheritance and Genetics Principles Demonstrated

- Punnett Square method
- Dihybrid cross with autosomal traits
- Analysis of simple dominant/recessive (E/e), with epistasis.

Comments and Variations

This problem can be simplified by making it into a monohybrid cross question. To do this, have students ignore the K and A loci, and focus entirely on the E locus.

Potentially Difficult Concepts

Students likely will be challenged by the fact they cannot know the alleles for certain, and must make some assumptions. It may help to tell them that genetic counselors see problems with no clear answers regularly. This problem is more like what they would encounter in their professional lives than a simple dihybrid cross.

Sample Problem 4

This problem shows how a series of questions of increasing difficulty can be constructed using a single dog as the model. The questions can be posed at different times over the course of a semester as students gain knowledge and skill.

Basic

1. Using the Evaluation Guide, what are the observable phenotypes for this dog?

   This is a formative assessment to ensure students can use the **Evaluation Guide** correctly. The genotype-related traits they should identify are:
   - Small overall size
   - Average skull shape
   - Legs short relative to body size
   - Long, straight hair that is not wiry
   - No facial furnishings
   - Folded ears (hard to identify here)
   - Tail is not visible, so is not informative
   - Coat color is pale blond yellow and white, with no agouti hairs visible.

2. Neither of the parents of this particular dog had long hair. Using a Punnett square, show how they could have produced this phenotype.

   Long hair is a homozygous recessive trait. This problem requires students to show how a monohybrid cross for two heterozygous parents can produce offspring that is homozygous for a recessive allele.

Intermediate

3. This dog came from a litter with 8 siblings. One sibling has short hair and is almost entirely black. What are the genotypes of the parents? Given those parents, would it be possible for one of the other siblings to be short haired but yellow? Show how you arrived at these answers.

   For this problem, the student must assess the coat length and color of the dog (e/e, l/l), and determine the potential genotypes of its sibling (E/-, L/-). Working backward they will need to identify the genotypes of parents (both must be E/e, L/l), and determine using Punnett square whether they could produce "e/e, L/-.")

Advanced

4. Type 1 rod-cone dysplasia is due to a defect in cGMP-specific phosphodiesterase 6B. The affected gene is on Chromosome 3, which also is where the IGFR1 locus is located.

   A. Based on chromosomal maps, how far apart are the two loci?

   B. This dog is a carrier for Type 1 rod-cone dysplasia. Given the distance between the two loci, what is the probability that the mutant IGFR-1 will separate from PPE6B in this dog's offspring?

   This problem is intended for students who have learned to locate genes in the OMIA database, and to calculate recombination frequencies based on gene distances. However, it also is a thought question, because to produce this small dog, BOTH copies of IGFR-1 must be mutated. Therefore the probability of the two alleles separating is zero.

Author and Image Credits

Problem 1:

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Problem 2:

Author(s): A. Daniel Johnson
Corrections: Jeffrey Jennings, Park School
Reference: Mosher, DS, et al. 2007. doi:10.1371/journal.pgen.0030079.
Images: **http://www.plosgenetics.org/article/info%3Adoi%2F10.1371%2Fjournal.pgen.0030079**

Problem 3:

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Problem 4:

Author(s): A. Daniel Johnson, Tiffany Blackburn
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Appendix B

What is our goal for the "Teaching Genetics with Dogs" project?

We hope to provide a broad-reaching, open-access library of word problems, reference materials, and links to news stories, tutorials, and other outside resources about dogs. Our goal is to have supporting materials for all of the core topics in typical undergraduate genetics courses, as well as general biology and non-majors biology. Our working list of topics is below.

We encourage instructors who teach general introductory genetics courses to review this working list and tell us if any essential concepts are missing. All instructors are welcome to send us suggestions for additional topics and resources they would like to see made available.

- Analysis Methods
  - Punnett square method
  - Probability method
  - Chi square test
  - Pedigree analysis
  - Phylogenetic analysis

- Inheritance Patterns
  - Mendelian monohybrid, dihybrid crosses
  - Incomplete dominance, co-dominance
  - Multiple alleles, allelic series
  - X-linked inheritance
  - Epistasis
  - Gene dosage effects
  - Pleiotropy
  - Mosaicism
  - Linkage, recombination, crossing over
  - Quantitative traits
  - Homozygous lethality

- DNA Structure and Regulation
  - Gain- and loss-of-function mutants
  - Genome and chromosome maps
  - Transposable genetic elements
  - Epigenetics
  - Mitochondrial inheritance

- Disease Genetics

  Gene sequences and underlying mutations for several hundred canine pathologies are available. They include:
  - X-linked diseases
  - Metabolic syndromes
  - Physical defects
  - Sensory loss (blindness and deafness)
  - Viral and prokaryote genetics can be taught using rabies, parvovirus, and Bordetella

- Evolutionary Genetics

  The complex history of dog domestication can demonstrate:
  - Comparative genomics (dogs vs. wolves)
  - Hardy-Weinberg equilibrium
  - Gene flow, bottlenecks, and isolation
  - Artificial selection and linkage disequilibrium