The color and patterning of pigmentation in cats, dogs, mice horses and other mammals results from the interaction of several different genes

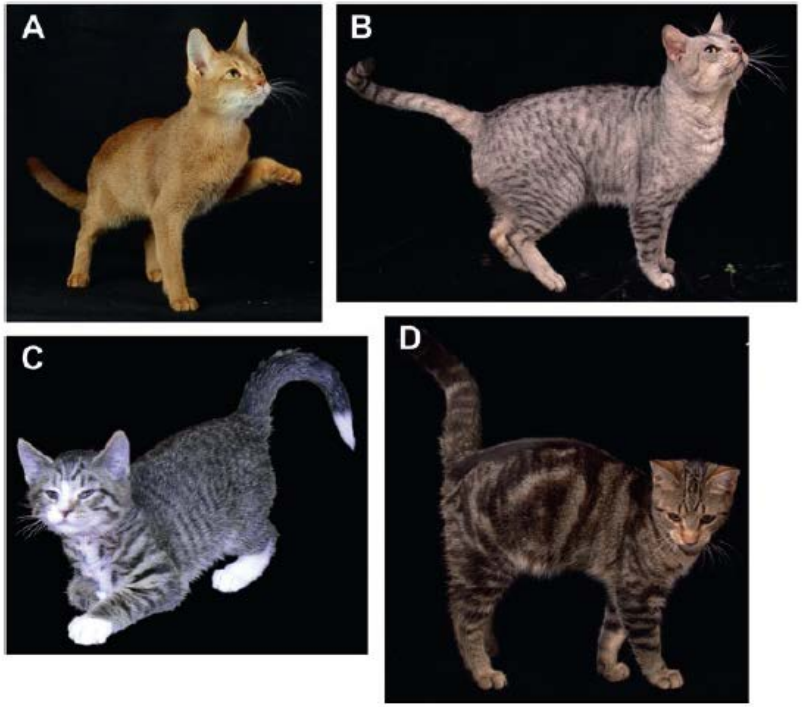
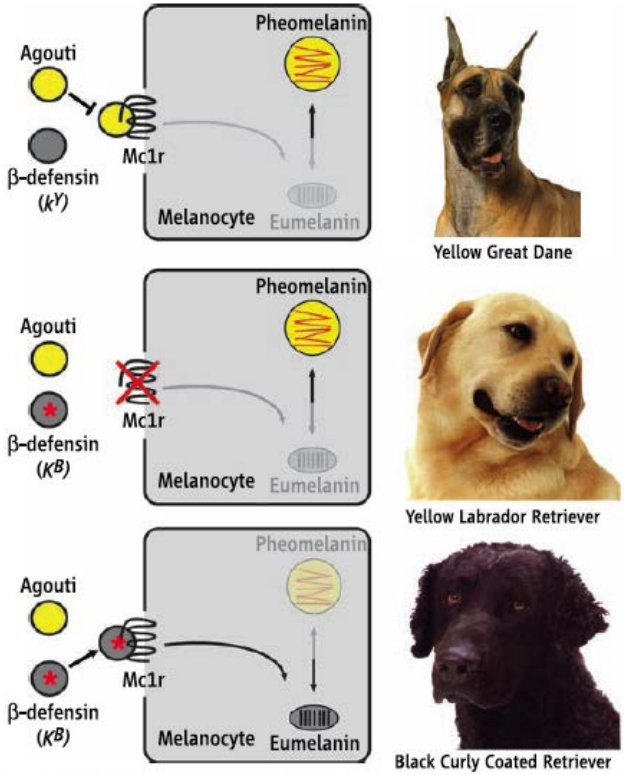


FIGURE 1.—Major coat pattern phenotypes of the domestic cat (*Felis silvestris catus*). A "hierarchy" of pelage patterns is observed in this species, with the absence of markings seen in Abyssinian cats (A) dominating over a spotted coat (B), which dominates over a "mackerel" (striped) coat (C), itself dominant over the blotched pattern (D). The classical, single-locus model for this phenotypic variation proposed the allelic series $T^a > T^s > T^M > t^b$ for these respective variants.



Production of yellow versus black pigment in dogs is controlled by three genes: *Mc1r*, *Agouti*, and *CBD103*. Dogs carrying wild-type alleles for all three genes have a yellow coat resulting from Agouti antagonism of Mc1r signaling in melanocytes (yellow Great Dane, top). Dogs carrying a loss-of-function mutation at *Mc1r* have a yellow coat, regardless of their genotype at *Agouti* or *CBD103* (yellow Labrador Retriever, middle). Dogs carrying wild-type alleles for *Mc1r* and *Agouti*, together with the *dominant black* allele of *CBD103* (K^B) have a black coat resulting from the interaction between a β-defensin and Mc1r (black Curly Coated Retriever, bottom).

Gene Interactions: *Specific alleles of one gene mask or modify (enhance, suppress or in some way alter) the expression of alleles of a second gene.*

Terms used to specify interactions between alleles of different genes:

Complementary gene action

- modified Mendelian ratio: AaBb X AaBb → 9:7 (2 genes, 2 alleles each, complete dominance)

Epistatic Gene Interactions

- epistatic (epistasis) (modified Mendelian ratio AaBb X AaBb → 9:4:3 for *recessive* epistasis assuming 2 genes, 2 alleles each, complete dominance)

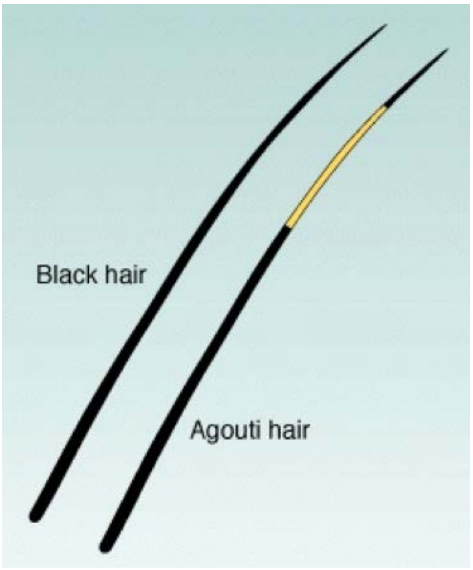
Modifiers & Suppressors (next lecture)

Allele interactions:

Terms used to specify interactions between alleles of the gene:

- Dominant/recessive incompletely dominant codominant


NSF
MOUSE: STRAIN 1
GENETIC BLUEPRINT
17 STRAINS



A	Agouti (A) is the colour of wild mice. The hair consists of a black base with yellow banding on each hair, producing the visual impression of a multi-hued brown.	 Agouti
a	Non-agouti mice (a/a) lack the yellow banding on the hairs, as in agouti mice (A/_), and therefore appear black. They may have white hairs on their sides and bellies.	

Black Swiss Mouse

A = agouti a = non agouti

B = black pigment b = brown pigment

C = pigmented c= non-pigmented (white or albino)

aaBBCC = black AABBCC = agouti

IN CLASS EXERCISE

Cross 1: Black X White #1 → Black → ¾ black ¼ white

Cross 2: Black X White #2 → Agouti →
9/16 agouti 3/16 black 4/16 white

Cross 3:
Black X White #3 → Agouti with spots→
27/64 spotted agouti 9/64 agouti 9/64 spotted black
3/64 black 16/64 white

Black Parent is the same in all three crosses:
aaBBCCs^{+}*s*$^{+}$ [s^{+} = not spotted S = spotted]

White parents are all true-breeding but are different in each cross. For each cross:

- ***first determine how many genes are segregating***
- ***then determine the genotype of the White parent***

Epistasis: **a form of gene interaction in which one gene interferes with the expression of another**

Epistasis:

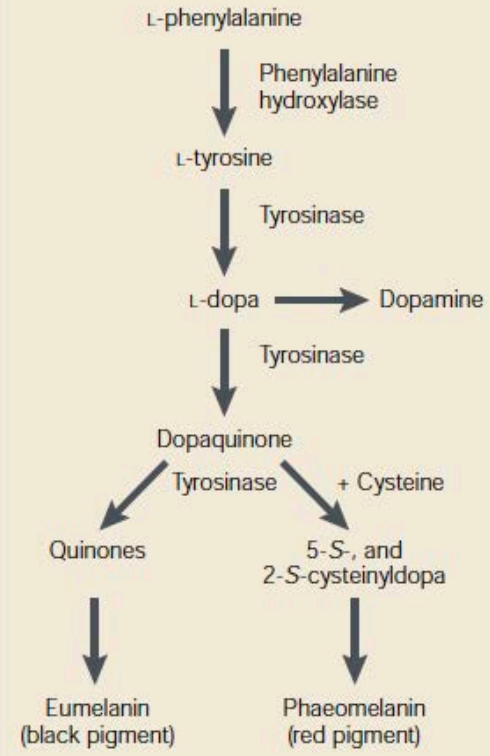
- a form of gene interaction in which one gene interferes with the expression of another (non-allelic) gene so that the phentype is governed by the former gene and not by the latter gene
- an allele of one gene "hides" or "masks" the effects of an allele of another gene
- *the cc allele in the homozygous state masks the expression of the other genes involved in pigment biosynthesis*

What is the molecular explanation for this phenomenology?

	Alleles	Function
A gene  **(agouti)**	***A*- yellow band on hair shaft** ***aa* yellow band absent** ligand for Mc1R (see below) inhibits synthesis of black/brown **a = loss of function**	**pigment distribution on hair shaft**
B gene	**B- black pigment** **bb brown pigment** ***modifier*** tyrosinase-Related Protein 1 (*TYRP1*) changes black to brown & no effect on red (molecular function unclear) **b = loss of function**	**pigment type**
C gene	**C- pigment present** **cc pigment absent** ***loss-of-function mutation epistatic to all other genes*** codes for tyrosinase (see below) **c = loss of function**	**presence or absence of pigment**

	ALLELES	FUNCTION
D gene (dilute)	**D- full expression of pigment** **dd diluted pigment** ***modifier*** *MLPH: MELANOPHILIN* *Affects melanosome distribution in the cell: dilutes black to grey and red to fawn* **d = loss of function**	**pigment intensity**
S gene spotted or splotch	**S- spots** **s^+s^+ no spots** affect melanocyte migration **S = dominant mutant allele**	**presence or absence of spots**

Box 1 | **Albinism — an unmodified trait?**



Albinism (oculocutaneous albinism type 1, OCA1), which results from the complete deficiency of the tyrosinase protein, is one of the few examples of a phenotype, the expression of which is constant regardless of genetic background. The tyrosine metabolic pathway is involved in the synthesis of eumelanin and phaeomelanin [85,86], and a deficiency of tyrosinase in this pathway results in the absence of these pigments, as well as reduced vision, nystagmus and photophobia. Mutant alleles that retain some activity result in hypopigmentation. The reason for its lack of modification is thought to result from the structure of the melanin synthesis pathway, the position of tyrosinase in this pathway and the nature of the molecular lesion (see figure). Tyrosinase catalyses three steps in this linear pathway that is thought to consist of only four steps. In the absence of tyrosinase, there are no metabolites that can act as targets for modification. The constancy of albinism resulting from tyrosinase deficiency is unique among phenotypic traits, suggesting that attributes of its function are unusual in mammalian biology and make it immune to genetic modifiers. It is striking that, although deficiency of tyrosinase results in a constant phenotype, mutations that affect the preceeding biochemical step, which converts phenylalanine to tyrosine, result in substantial phenotypic variability[4,5].

http://www.euronet.nl/users/hnl/afb2.htm

pheomelanin = red or yellow

eumelanin = **black or brown**

Want to see some biochemistry?

Go to link below figure

From Gene to Phenotype: While we are thinking about tyrosinase
Temperature Sensitive Proteins and the Siamese Cat

Note this example does NOT relate to epistasis

TYR (tyrosinase) gene corresponds to the colour locus in cats and its alleles, from dominant to recessive, are as follows: ***C (full colour) > cs (siamese) > c (albino)***

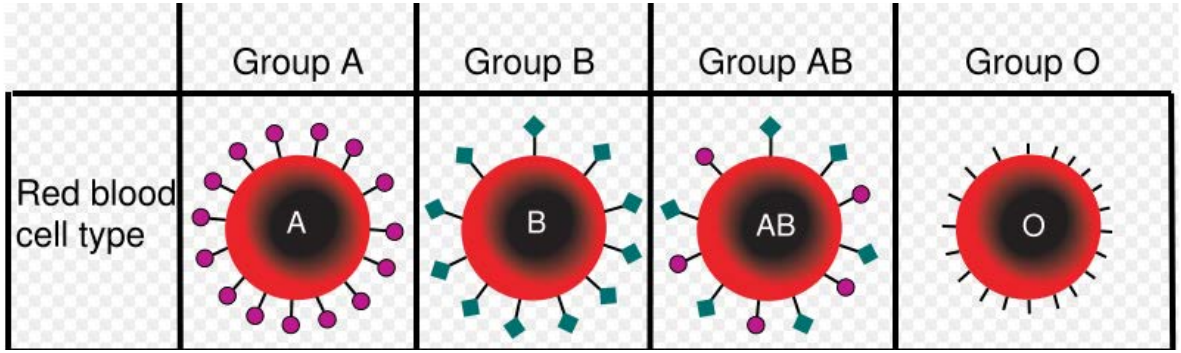
Temperature sensitive allele: ***A conditional mutation***
that produces the mutant phenotype in one (restrictive or non-permissive) temperature range and the wild-type phenotype in anc temperature range (see also pg 217 of text)

The tyrosinase gene product specified by temperature sensitive mutations of the C gene ***(cb and cs)*** is only active at lower body temperatures. What this means is that on the parts of the cat where the temperature of the hair follicles is high, the gene product is inactive or less active, resulting in less pigment. However, on the points (ears, nose, feet and tail), where the temperature is slightly cooler, the mutant tyrosinase is active and pigmentation is darker. The difference between siamese, burmese and balinese is the degree to which the tyrosinase protein is shut off at the normal body temperature.

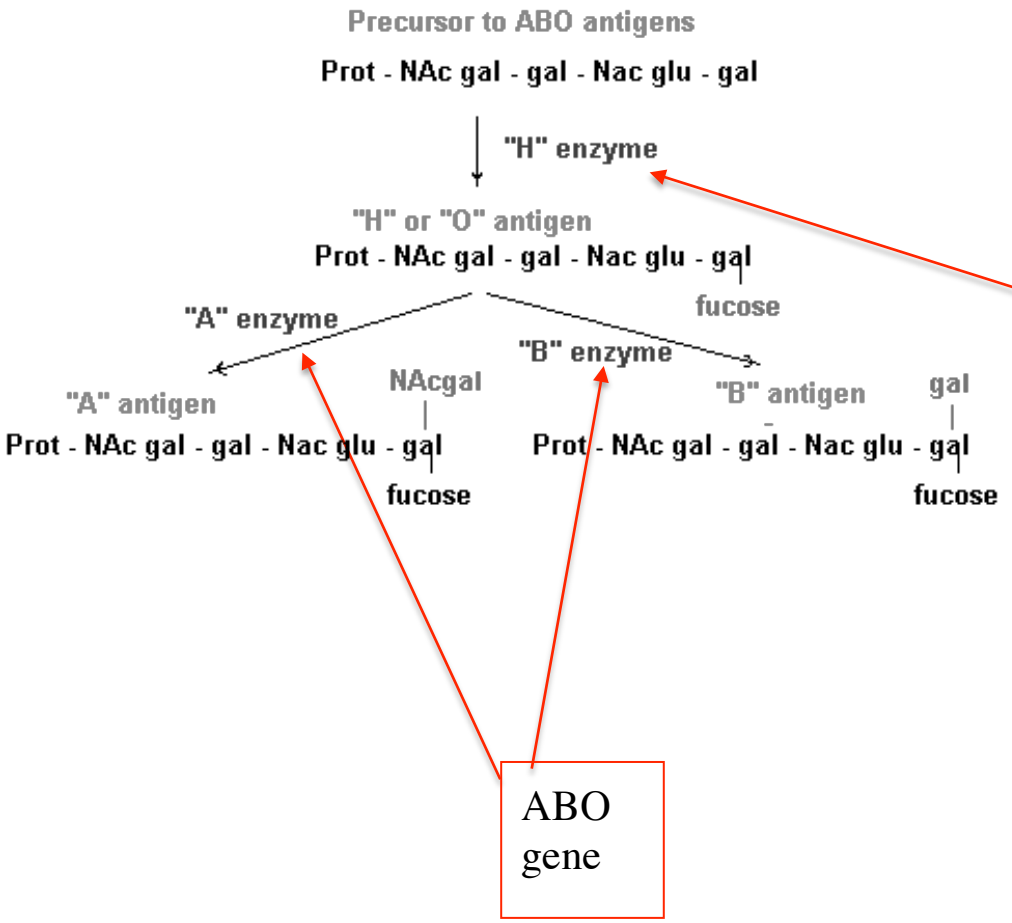
The coat color examples considered above focus on easily visualized phenotypes such as pigmentation

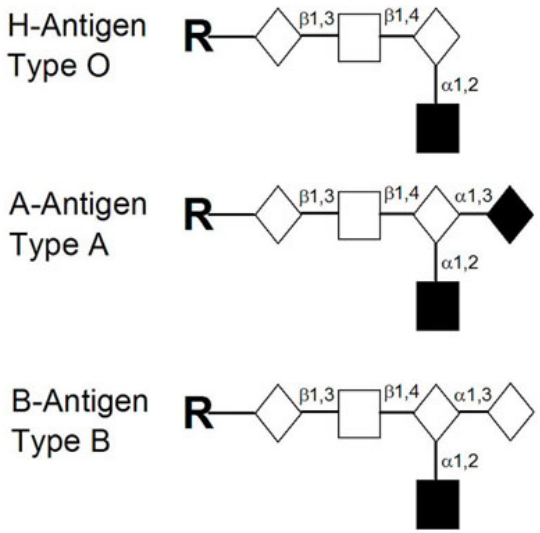
It is important to keep in mind, though, that the same principles apply to all traits whether they relate to morphology or physiology or developmental processes.

ABO blood group genetics: A and B alleles are codominant to each other and completely dominant to O (which is a loss-of-function allele)



In the assessment of ABO blood group type:
O means not A and not B





REMEMBER:
O means not A and not B (this is important)

In a 1945 trial, a California woman accused Charlie Chaplin of fathering her child

By far J. W. Sandison's most famous photograph is of a Charlie Chaplin look-alike contest taken on November 5, 1921, a Saturday afternoon, outside the Liberty Theatre on W. Holly Street. Each of the more than 80 participants who dressed the part received free admission (a 10-cent value) to see Chaplin's latest comedy The Idle Class. First prize for best costume and "Chaplin walk" was a 5-lb. box of chocolates and $2.50 cash. The photograph has appeared around the world in numerous books, magazines and television documentaries.
Whatcom Museum #203

In a 1945 trial, a woman accused Charlie Chaplin of fathering her child. The ABO blood types were as follows:

	Phene	Genotype	Revised genotype
woman	A		
Chaplin	O		
child	B		

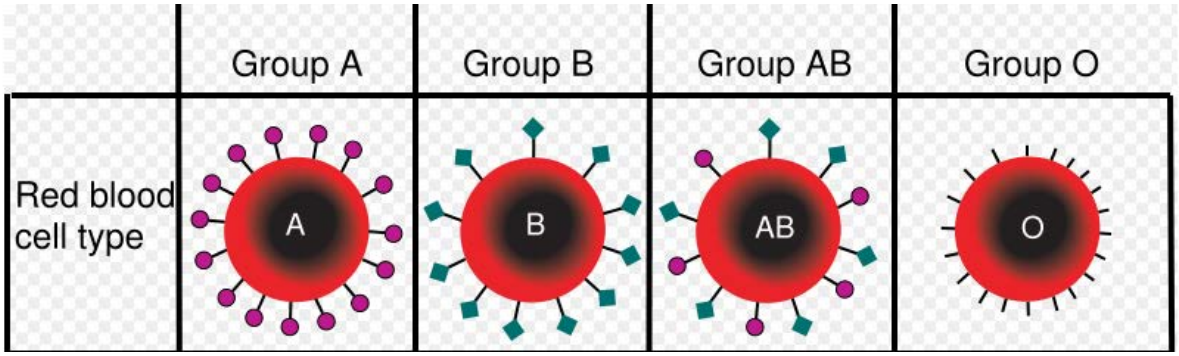
When the California jury declared that Chaplin was the father of the child, the *Boston Herald* commented:

"***California has in effect decided that black is white, two and two are five, and up is down.***"

Do you agree with the jury or with the press?
Can you use the principle of epistasis **to rescue the "reputation" of the jury system?**

Infidelity or Epistasis?
The Bombay Phenotype

	Phenotype	Genotype	Revised genotype
woman	A		
Chaplin	O		
child	B		

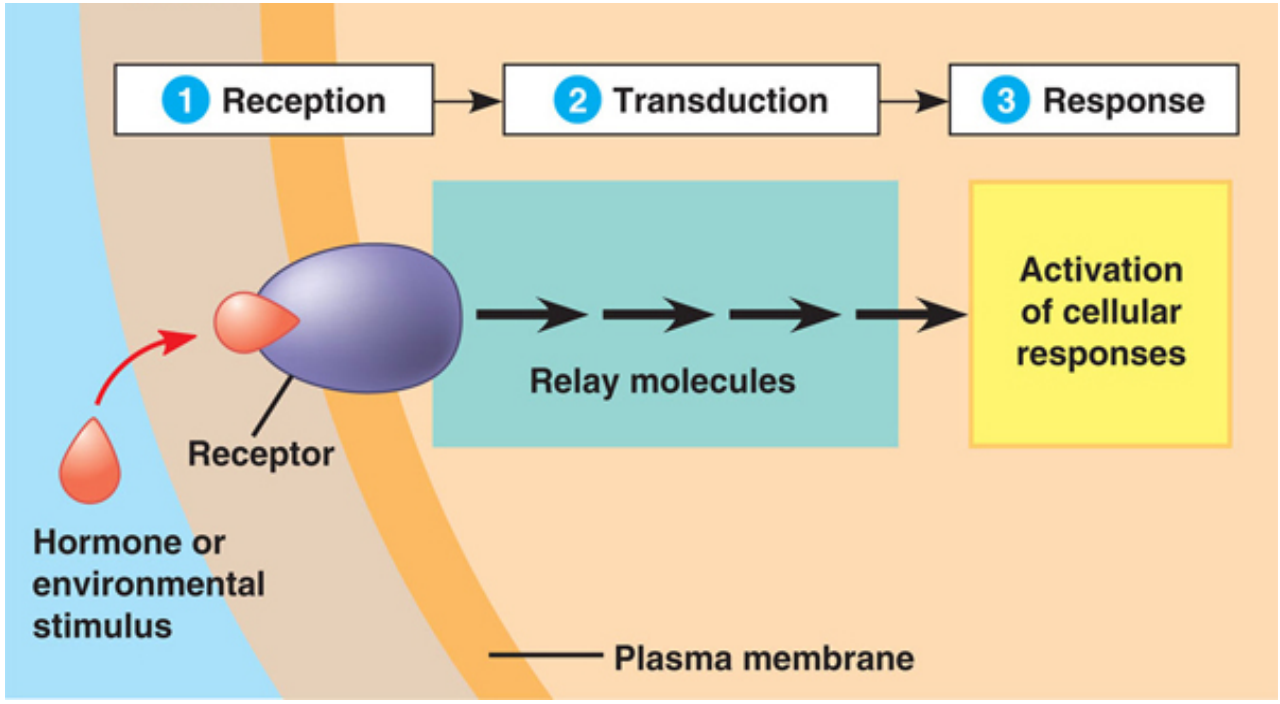


Bombay genotype = hh

genotype frequency in Bombay = $1x10^{-4}$
genotype frequency in northern Europe = $1x10^{-6}$

Required part of lecture ends HERE

OPTIONAL INTERESTING STUFF (next few pages)



Melanocortin 1 receptor (MC1R aka extensin)

(variant alleles of this gene cause red hair in humans)

MC1R interacts with:

- ***melanocyte stimulating hormone*** (not shown on next page) – causes eumelanin to be synthesized predominantly
- ***agouti signalling peptide*** – inhibits Mc1r and causes synthesis of yellow melanins
- ***β defensin = K locus***: K^B dominant to k^y

The Agouti gene product downregulates tyrosinase which acts at more than one point in the melanin biosynthetic pathway. The synthesis of black/brown pigments is affected more by agouti than red/yellow pigments for reasons that aren't entirely clear (and there were contradictory explanations in different references……)

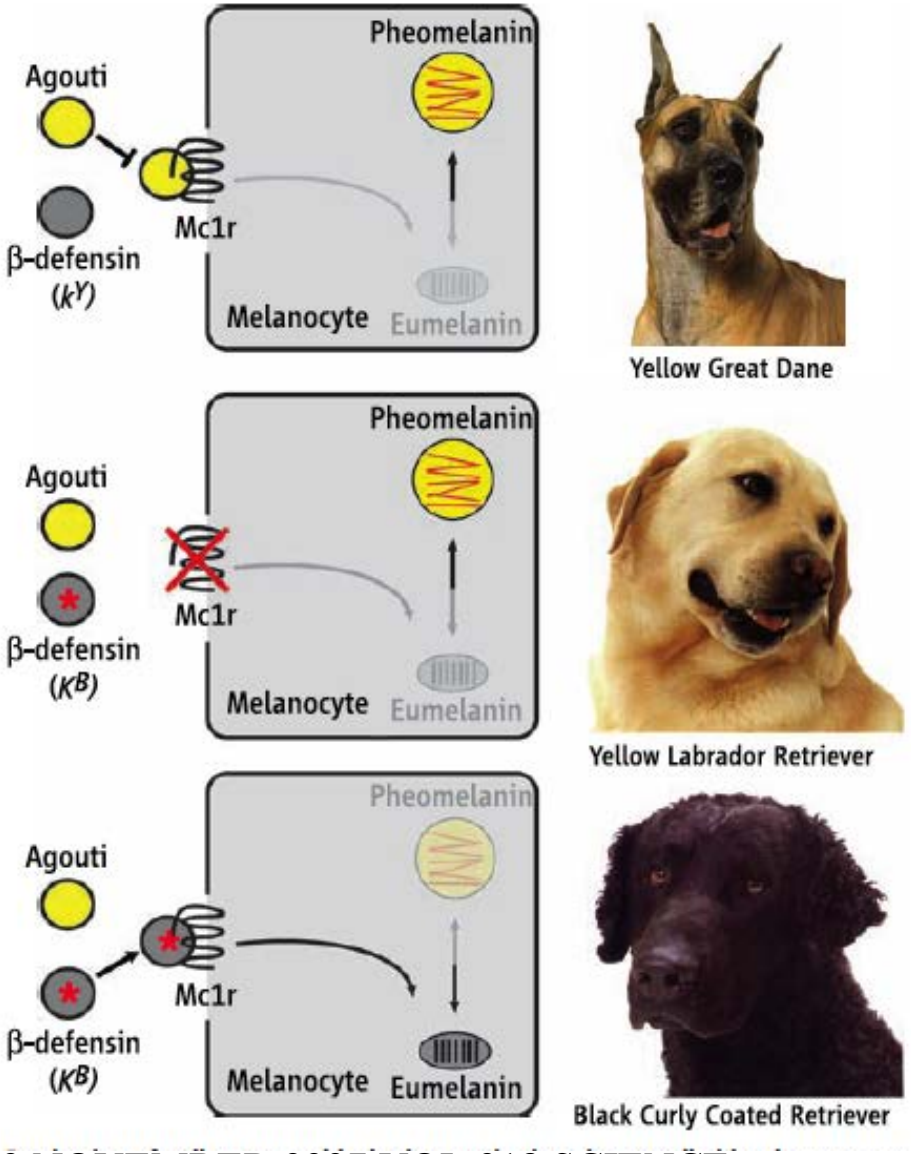
INFO for figure on the next page

30 NOVEMBER 2007 VOL 318 SCIENCE

Genetic analysis of mammalian color variation has provided fundamental insight into human biology and disease. In most vertebrates, two key genes, Agouti and Melanocortin 1 receptor (Mc1r), encode a ligand-receptor system that controls pigment type-switching, but in domestic dogs, a third gene is implicated, the K locus, whose genetic characteristics predict a previously unrecognized component of the melanocortin pathway. We identify the K locus as β -defensin (CBD103) and show that its protein product binds with high affinity to the Mc1r and has a simple and strong effect on pigment type-switching in domestic dogs and transgenic mice. These results expand the functional role of b-defensins, ***a protein family previously implicated in innate immunity***, and identify an additional class of ligands for signaling through melanocortin receptors.

Legend to figure on the next page

Production of yellow versus black pigment in dogs is controlled by three genes: Mc1r, Agouti, and CBD103 (aka β-defensin). Dogs carrying wild-type alleles for all three genes have a yellow coat resulting from Agouti antagonism of Mc1r signaling in melanocytes (yellow Great Dane, top). Dogs carrying a loss-of-function mutation at Mc1r have a yellow coat, regardless of their genotype at Agouti or CBD103 (yellow Labrador Retriever, middle). Dogs carrying wild-type alleles for Mc1r and Agouti, together with the dominant black allele of CBD103 (KB) have a black coat resulting from the interaction between a b-defensin and Mc1r (black Curly Coated Retriever, bottom).

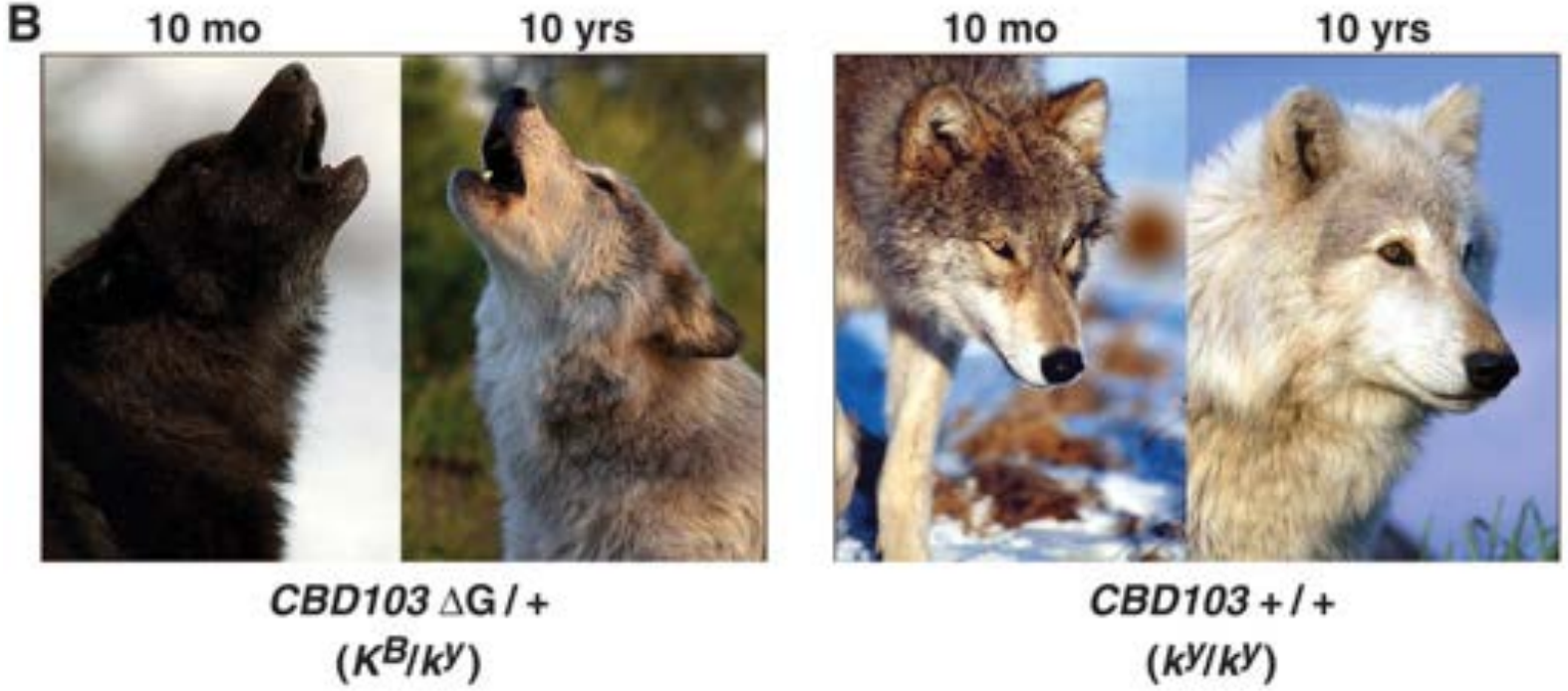


30 NOVEMBER 2007 VOL 318 SCIENCE

Legend to figure is on the previous page.

What kind of gene interaction is seen in the Labrador ?

The K^B allele is found in melanistic wolves



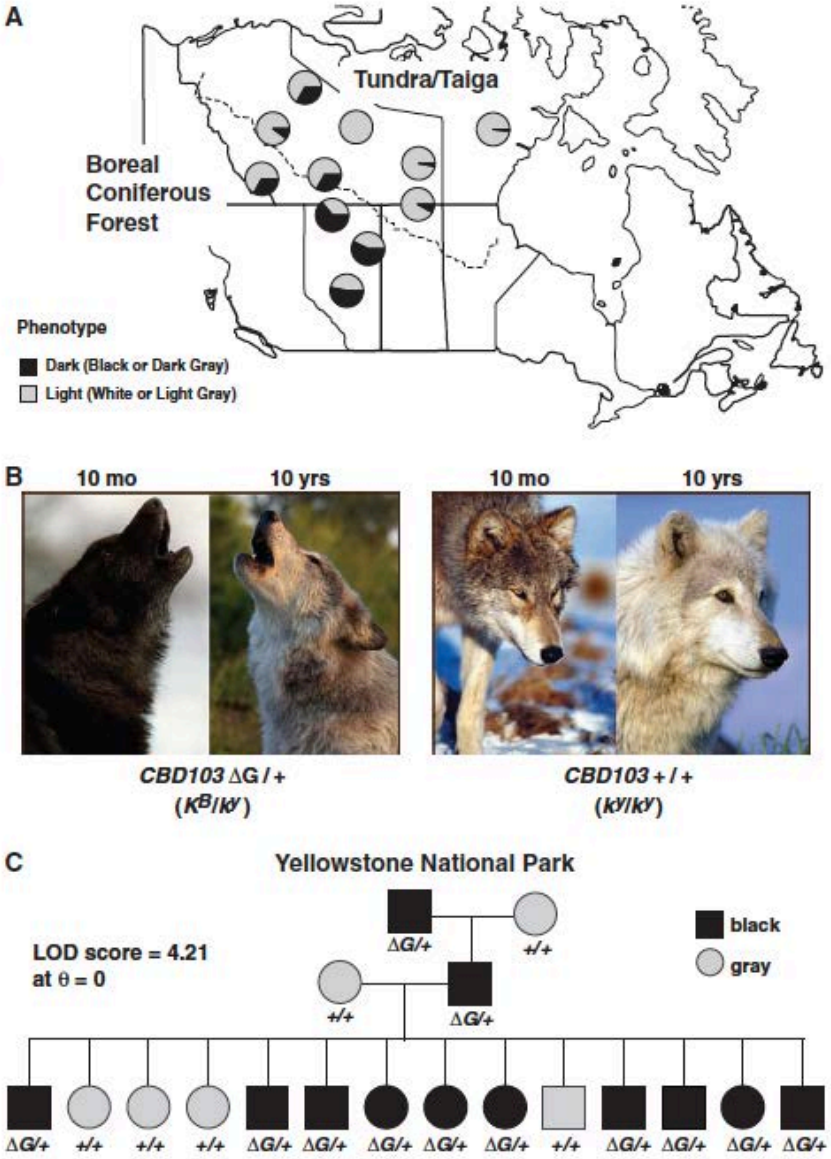


Fig. 1. Distribution of melanism and *K* locus genotypes in North American gray wolves. (**A**) Location and coat color phenotype of Canadian samples used here and as described (*4*). (**B**) Age-related graying and the associated difficulty of inferring genotype from phenotype in gray animals. Each pair of photos shows the same individual at different ages (10 months and 10 years) and documents an increasingly gray appearance at 10 years, reflecting the dilution of eumelanin in the K^B/k^y individual (left pair of images) and dilution of both eumelanin and pheomelanin in the k^y/k^y individual (right pair of images). [Images courtesy of Monty Sloan, Wolf Park, Battle Ground, Indiana] (**C**) Co-segregation of K^B and black coat color in a three-generation pedigree from the Leopold pack in Yellowstone National Park (*17*). Δ*G* indicates the dominant K^B allele, whereas + indicates the wild-type allele, k^y.