Chapter 13

Extensions of Mendelian Genetic Principles

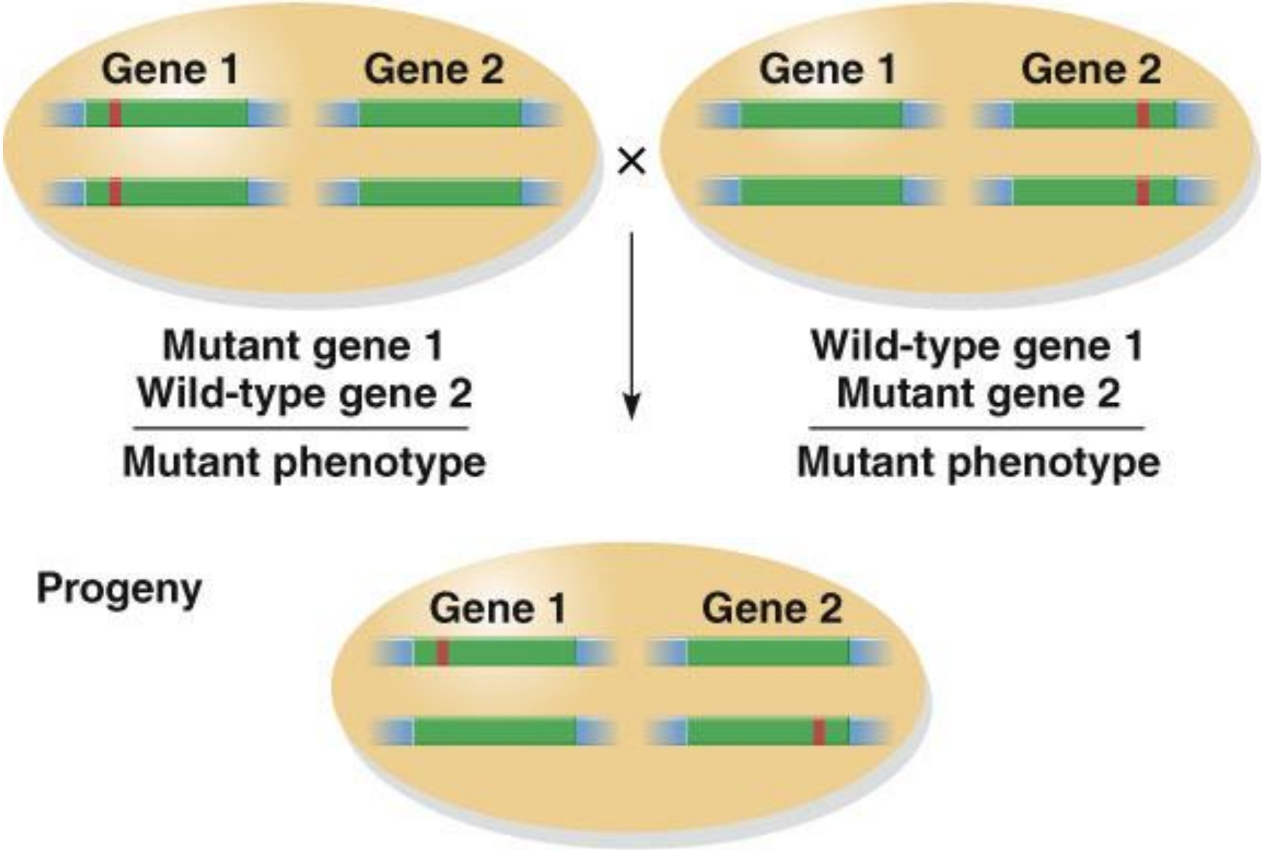
Number of Genes for Mutations of the Same Phenotype

- For a given mutation we have assumed up until now that all mutations for a certain trait are in the same gene.
  - However, mutations in several different genes can lead to the same or similar phenotypes.
- When performing a genetic analysis it is important to know if one or more genes might be involved.
  - We use the **complementation** test to determine how many genes are present.

Complementation Test

- Determines if two independently isolated mutations with the same phenotype have affected the same or different genes.
- The two mutants are crossed with one another, two outcomes are possible:
  - The progeny are mutant…**no complementation** so the same gene is affected.
  - The progeny are wild-type…**complementation** has occurred so the mutations must be in two different genes.

a) Mutations in different genes: complementation



Parents

Mutant gene 1
Wild-type gene 2

Mutant phenotype

Wild-type gene 1
Mutant gene 2

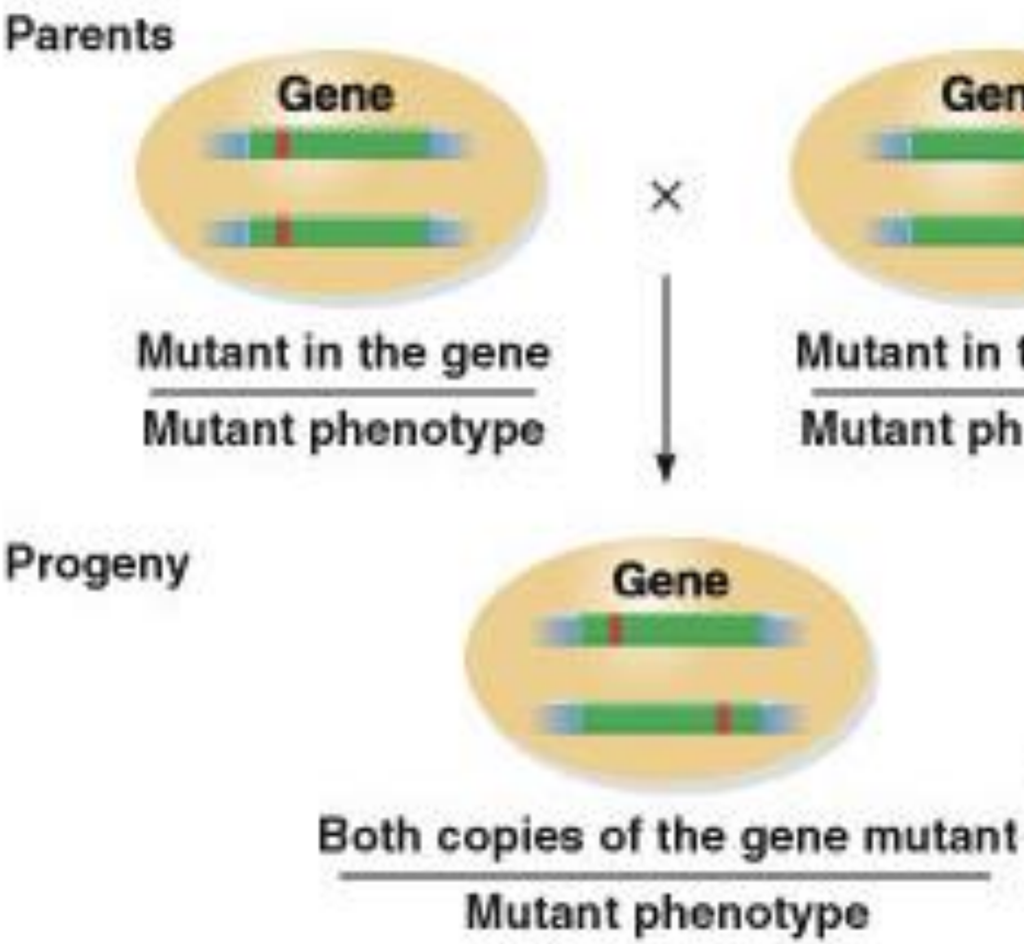
Mutant phenotype

Progeny

Wild-type gene 1
Mutant gene 1
Wild-type gene 2
Mutant gene 2

Wild-type phenotype

b) Mutations in the same gene: no complementation



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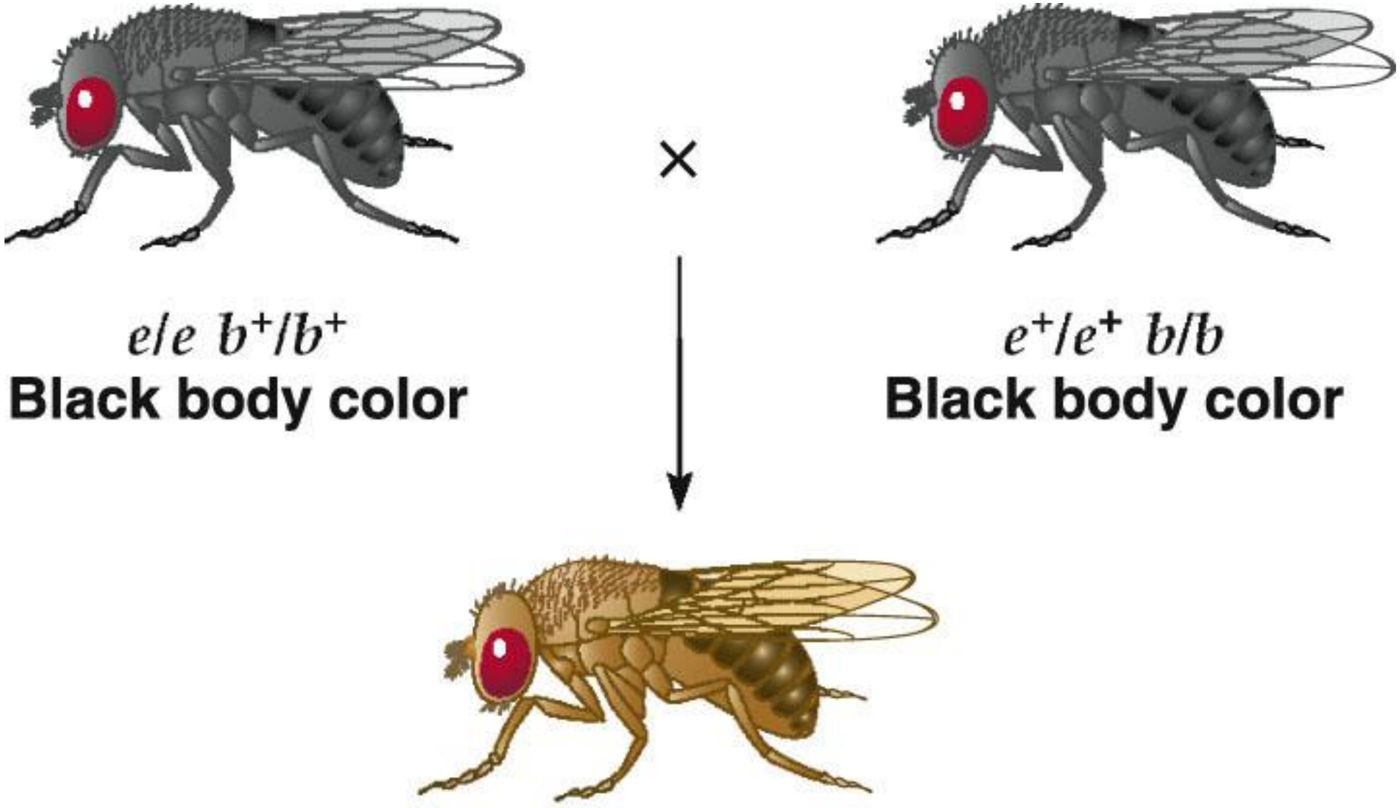


$e/e\ b^+/b^+$
Black body color

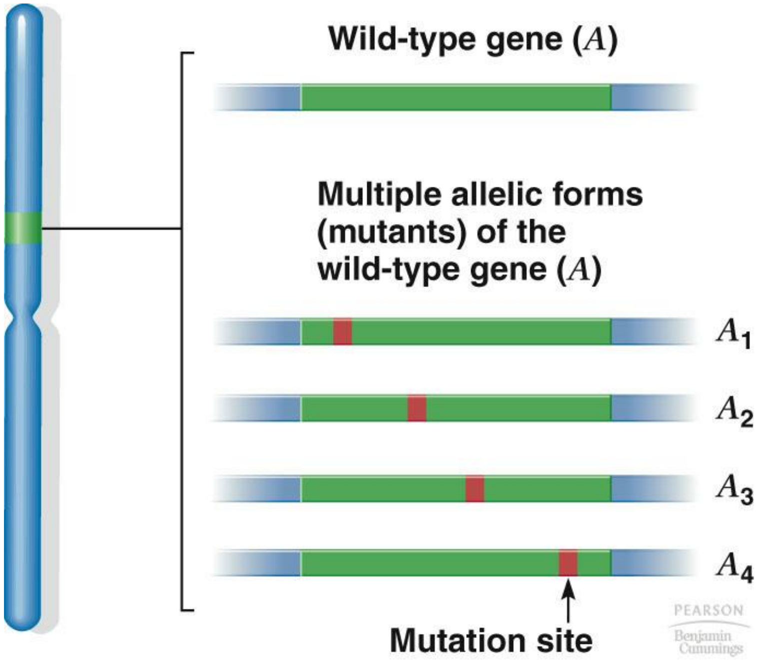
×

$e^+/e^+\ b/b$
Black body color

$e^+/e\ b^+/b$
Wild-type body color resulting from complementation of the two mutant genes

Multiple Alleles

- So far we have only considered genes with two alleles.
  - One mutant form and the other wild-type.
- Some genes may have a wild-type form and more than one mutant form.
  - These genes are said to have **multiple alleles**.
- Importantly, for all diploid individuals, it is only possible to have two of these alleles present.



ABO Blood Groups

- An example of multiple alleles is the **ABO blood group.**
- Discovered by Karl Landsteiner in the early 1900's.
  - Won 1930's Nobel Prize for Physiology or Medicine.
- Important for the transfusion of blood from one person to another.
  - Important to realize that other blood compatibility factors are present as well.

ABO Blood Group

- There are four blood group phenotypes:
  - O, A, B and AB.
  - Different combinations of the alleles i, i^A and i^B give rise to the four phenotypes.

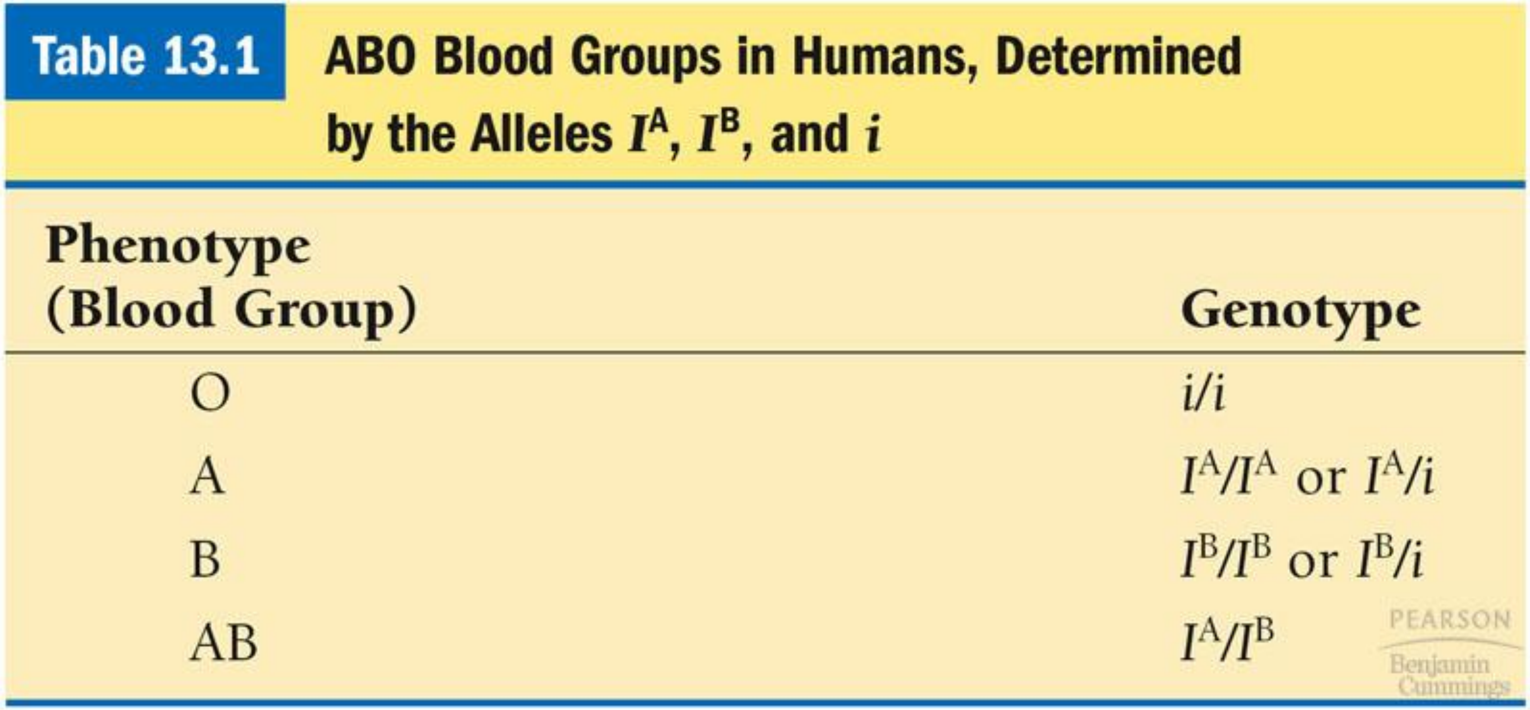


Table 13.1 **ABO Blood Groups in Humans, Determined by the Alleles I^A, I^B, and i**

Phenotype (Blood Group)	Genotype
O	i/i
A	I^A/I^A or I^A/i
B	I^B/I^B or I^B/i
AB	I^A/I^B

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ABO Blood Group

- i^A and i^B are dominant to i.
- i^A and i^B are codominant to one another.
- A child that is type O has parents that are:

- A child that is type AB, has parents that are:

Use of ABO Blood Groups in Paternity Cases

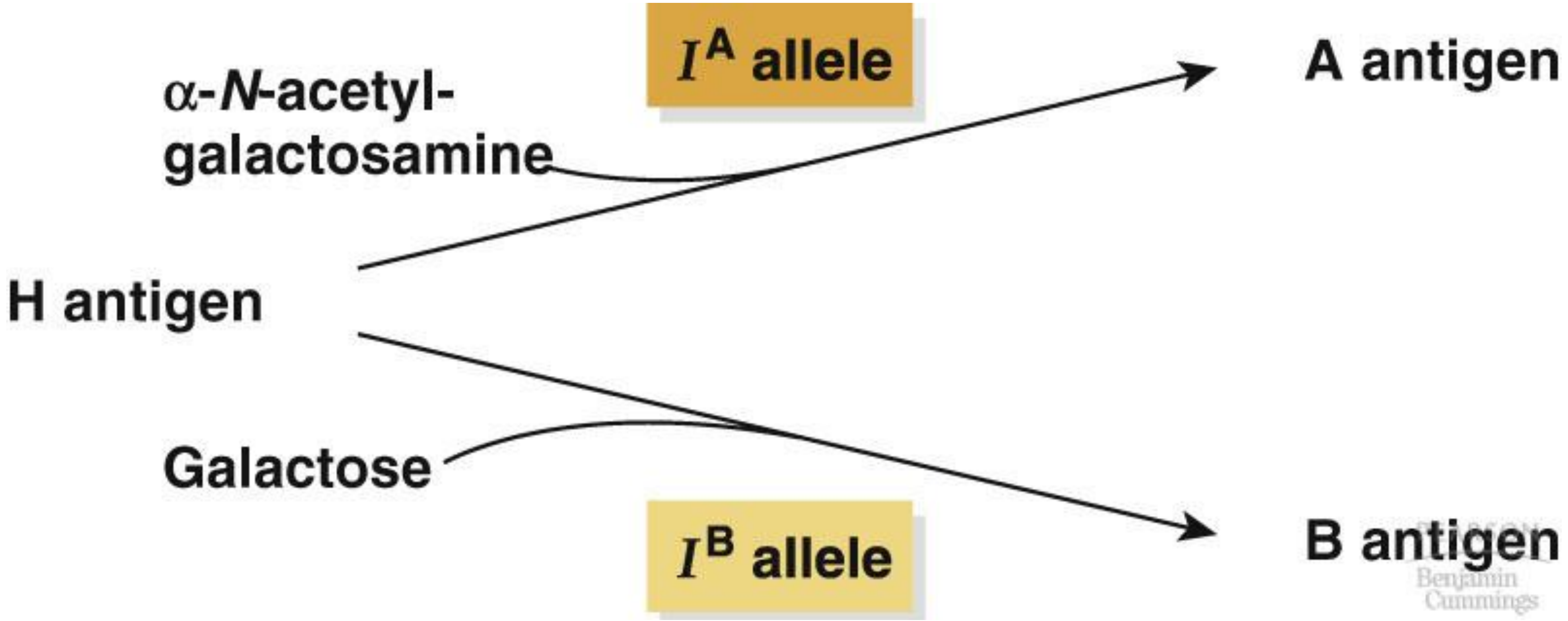
- Before DNA typing, the ABO blood locus was used to determine cases of paternity.
- A man with type O blood is thought to be the father of a child with type AB blood.
  - Not possible since the child had to receive i^A and i^B from his two parents. The father is ii.
- Blood typing can never determine if a man is the father of a child, but it can eliminate the possibility that he is the father of the child.

The Nature of the ABO Blood Groups

- Red blood cells (RBCs) contain complex polysaccharides linked to the lipids in their membranes.
  - These polysaccharides are on the outside of the RBCs.
  - These are **antigens**, since in organisms where this molecule is foreign, **antibodies** will be produced against it.
- People with type A blood have A antigens on their RBCs, while type B individuals have type B antigens. Type AB individuals have both A and B antigens present on their RBCs.

The Nature of the ABO Blood Groups

- ABO locus encodes **glycosyltransferases**, enzymes that add sugar groups to existing polysaccharides.
- RBCs have a precursor glycolipid called the **H antigen** present.
  - The A allele produces a glycosyltransferase enzyme that adds a **α-N-acetylgalactosamine** to the H antigen.
    - Produces the A antigen.
  - The B allele produces a different glycosyltransferase that adds **galactose** to the H antigen.
    - Produce the B antigen.
  - Type O individuals lack these glycosyltransferase enzymes, so the H antigen is unmodified.



α-*N*-acetyl-galactosamine

I^A allele

A antigen

H antigen

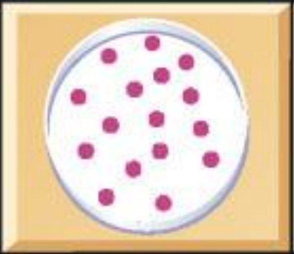
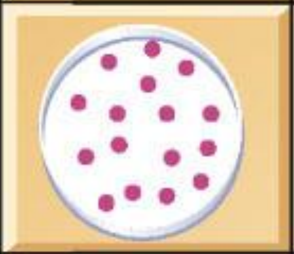
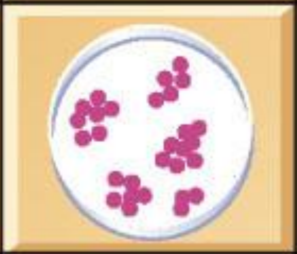
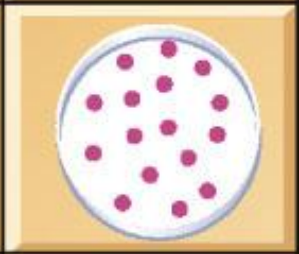
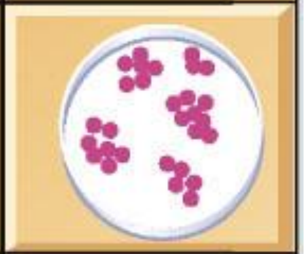
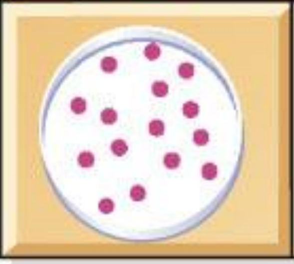
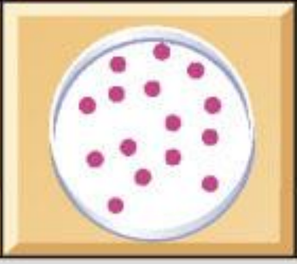
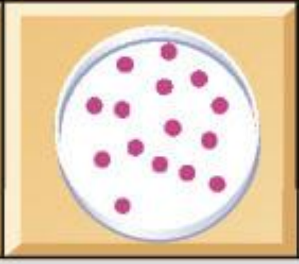
Galactose

I^B allele

B antigen

Antibodies to the ABO Antigens

- People with blood type O
  - Have anti-A and anti-B antibodies
- People with blood type A
  - Have anti-B antibodies
- People with blood type B
  - Have anti-A antibodies
- People with blood type AB
  - Have not antibodies to A or B
- What about the H antigen?
  - It is shared amongst all these individuals so antibodies are not raised against this antigen.

Serum from blood type	Antibodies present in serum	Cells from blood type			
		O	A	B	AB
O	Anti-A Anti-B				
A	Anti-B				
B	Anti-A				
AB	—				

The H Antigen

- The H antigen is produced by the *H* allele at a distinct locus from the ABO locus.
- People who are homozygous h/h do not make the H antigen.
  - Regardless of ABO locus, these individuals are similar to blood type O individuals.
    - They lack the A and B antigens.
  - Produce **anti-O antibodies** (antibodies against the H antigen).
  - These people have the **Bombay** phenotype.

Drosophila Eye Colour: Multiple Alleles

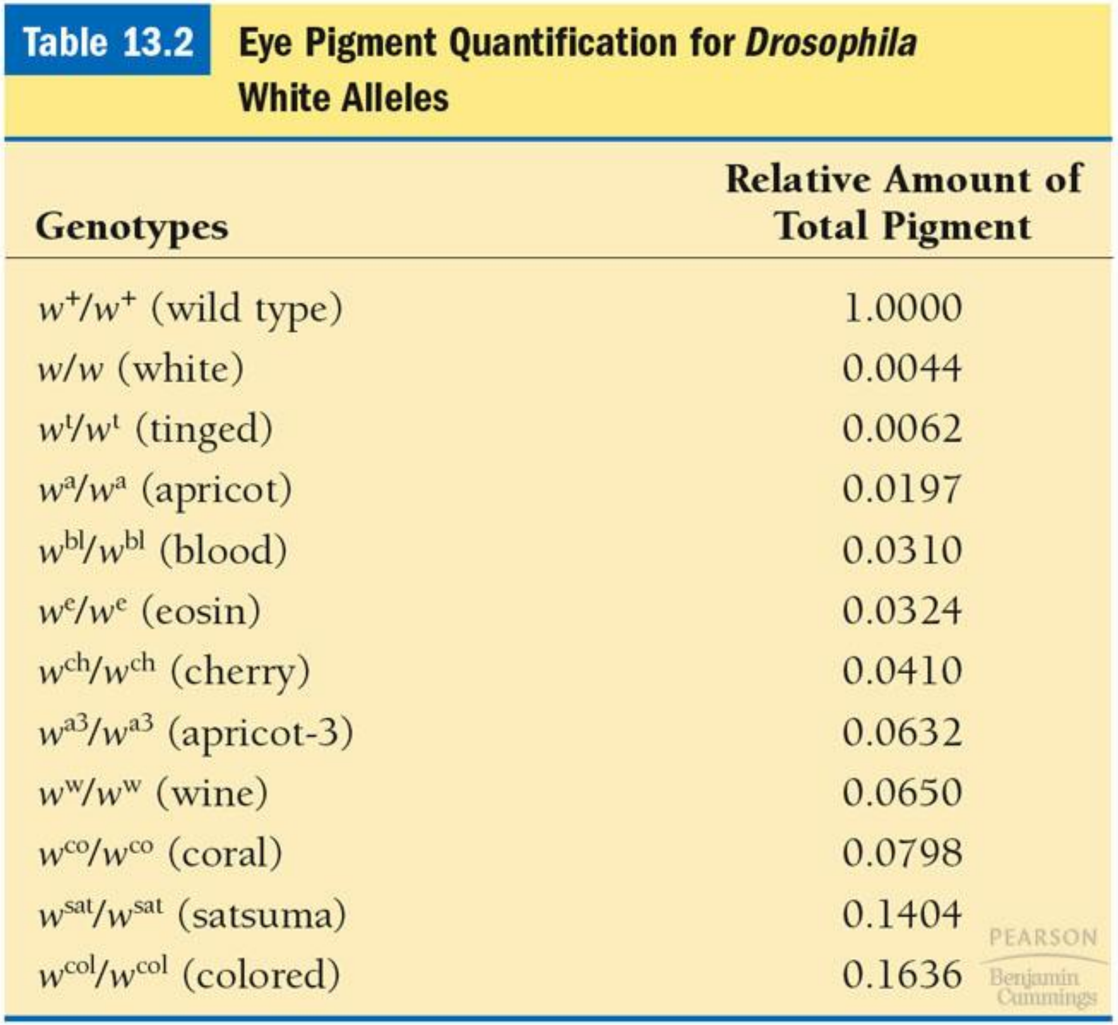
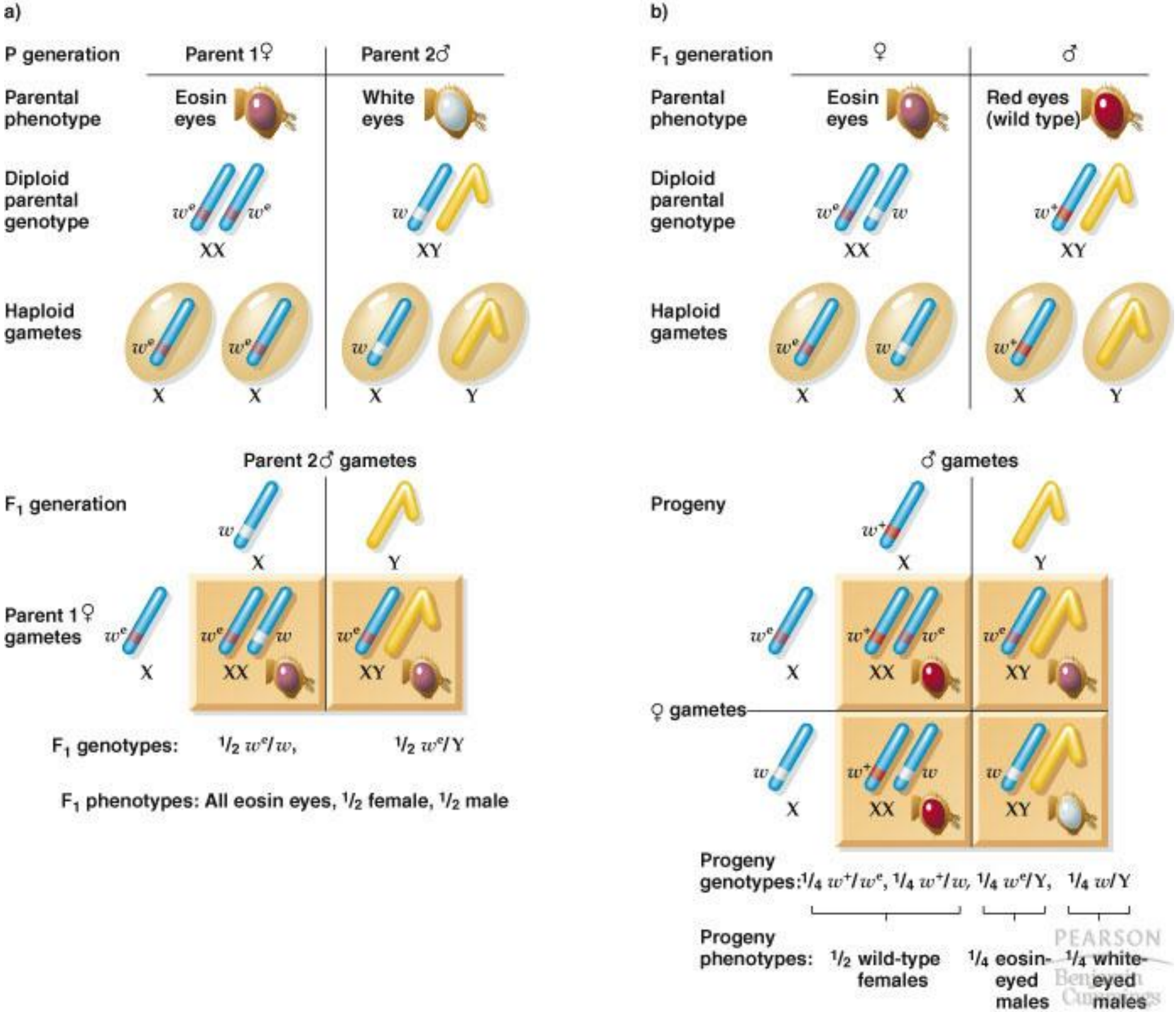


Table 13.2 **Eye Pigment Quantification for *Drosophila* White Alleles**

Genotypes	Relative Amount of Total Pigment
w^+/w^+ (wild type)	1.0000
w/w (white)	0.0044
w^t/w^t (tinged)	0.0062
w^a/w^a (apricot)	0.0197
w^{bl}/w^{bl} (blood)	0.0310
w^e/w^e (eosin)	0.0324
w^{ch}/w^{ch} (cherry)	0.0410
w^{a3}/w^{a3} (apricot-3)	0.0632
w^w/w^w (wine)	0.0650
w^{co}/w^{co} (coral)	0.0798
w^{sat}/w^{sat} (satsuma)	0.1404
w^{col}/w^{col} (colored)	0.1636


a)
P generation
Parent 1♀
Parent 2♂
Parental phenotype
Eosin eyes
White eyes
Diploid parental genotype
w^e
w^e
XX
w
XY
Haploid gametes
w^e
X
w^e
X
w
X
Y
Parent 2♂ gametes
F₁ generation
w
X
Y
Parent 1♀ gametes
w^e
X
w^e
w
XX
w^e
XY
F₁ genotypes: 1/2 w^e/w, 1/2 w^e/Y
F₁ phenotypes: All eosin eyes, 1/2 female, 1/2 male
b)
F₁ generation
♀
♂
Parental phenotype
Eosin eyes
Red eyes (wild type)
Diploid parental genotype
w^e
w
XX
w^+
XY
Haploid gametes
w^e
X
w
X
w^+
X
Y
♂ gametes
Progeny
w^+
X
Y
w^e
X
w^+
w^e
XX
w^e
XY
♀ gametes
w
X
w^+
w
XX
w
XY
Progeny genotypes: 1/4 w^+/w^e, 1/4 w^+/w, 1/4 w^e/Y, 1/4 w/Y
Progeny phenotypes: 1/2 wild-type females
1/4 eosin-eyed males
1/4 white-eyed males
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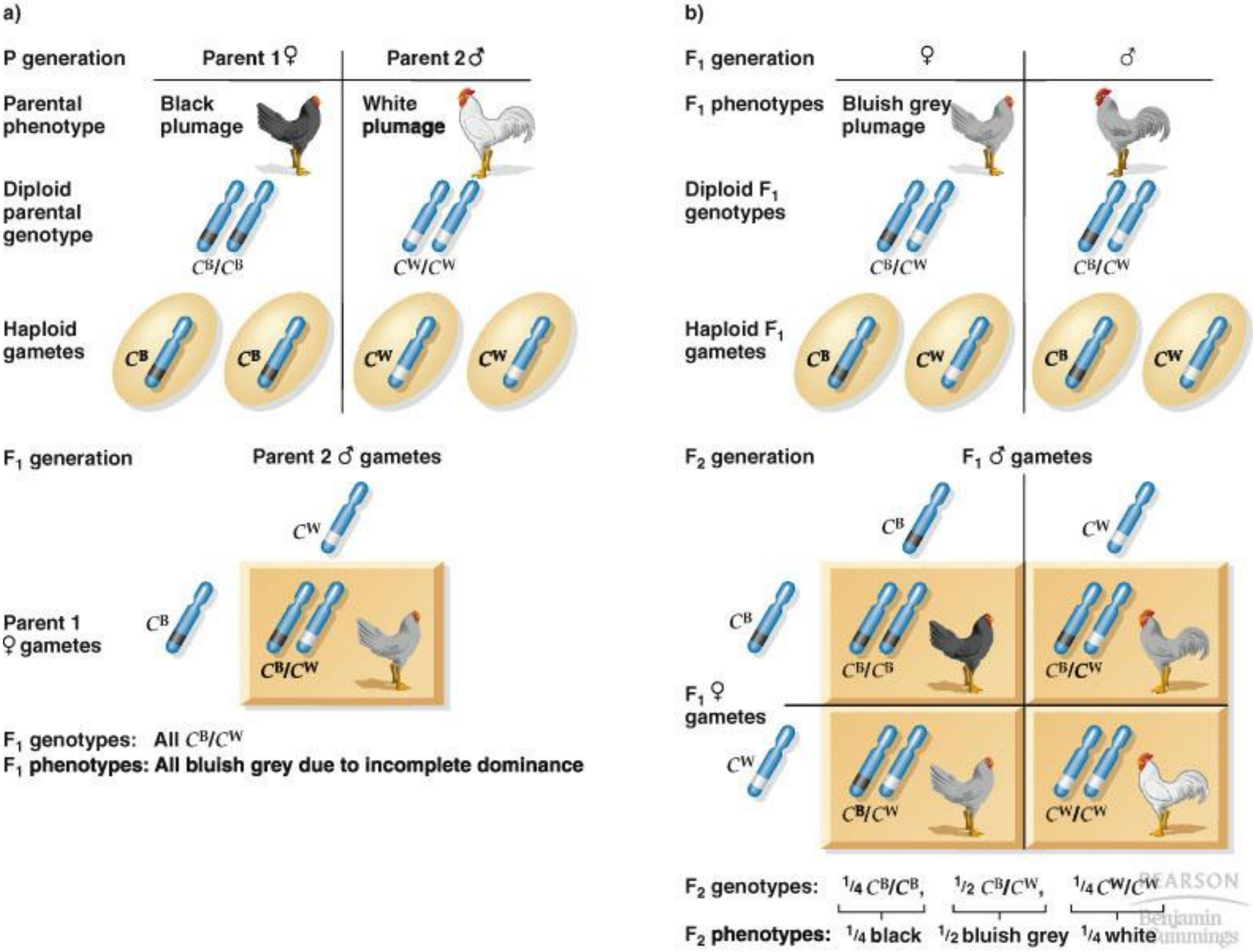
Incomplete Dominance

- When one allele is not completely dominant to another then it is said to show **incomplete** or **partial dominance**.
- The phenotype of the heterozygote is **intermediate** to those of the homozygotes.
- Classic example:
  - Flower colour in snapdragons:
    - Red flowered (C^R/C^R) x White flowered (C^W/C^W)
      - Progeny are all pink flowered (C^R/C^W)

Plumage Colour in Chickens: Incomplete Dominance

- Crosses between truebreeding **black** (C^BC^B) and **white** (C^WC^W) birds produces an F_1 that is bluish-grey (C^BC^W) called an **Andulasian**.
- An Andulasian crossed to another Andulasian produces:
  - 1 black: 2 Andulasian: 1 white fowl.


a)
P generation
Parent 1 ♀
Parent 2 ♂
Parental phenotype
Black plumage
White plumage
Diploid parental genotype
C^B/C^B
C^W/C^W
Haploid gametes
C^B
C^B
C^W
C^W
F₁ generation
Parent 2 ♂ gametes
C^W
Parent 1 ♀ gametes
C^B
C^B/C^W
F₁ genotypes: All C^B/C^W
F₁ phenotypes: All bluish grey due to incomplete dominance
b)
F₁ generation
♀
♂
F₁ phenotypes
Bluish grey plumage
Diploid F₁ genotypes
C^B/C^W
C^B/C^W
Haploid F₁ gametes
C^B
C^W
C^B
C^W
F₂ generation
F₁ ♂ gametes
C^B
C^W
F₁ ♀ gametes
C^B
C^W
C^B/C^B
C^B/C^W
C^B/C^W
C^W/C^W
F₂ genotypes: $\frac{1}{4}$ C^B/C^B, $\frac{1}{2}$ C^B/C^W, $\frac{1}{4}$ C^W/C^W
F₂ phenotypes: $\frac{1}{4}$ black $\frac{1}{2}$ bluish grey $\frac{1}{4}$ white
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Palomino Horses: Incomplete Dominance

- **Palominos** do not breed true when bred together:
  - Progeny are 1/4 cremellos (extremely light colored), 1/2 palominos and 1/4 light chestnuts.
  - 1:2:1 ratio is characteristic of incomplete dominance.
- C/C produces a horse that is light chestnut (or sorrel), C/C^{cr} palamino, and C^{cr}/C^{cr} the cremello.
  - Other coat color genes are necessary but are at different loci.
  - It is thought that there up to 7 different loci that contribute to the coat color of horses.
- In other words the palamino is a slight **dilution** of the sorrel, and the cremello is a further dilution to give an even paler colour.

Codominance

- The heterozygote displays **both** phenotypes of the two homozygotes.
  - Incomplete dominance displayed intermediate phenotype between the two homozygotes.
- The **ABO blood group** i^A and i^B alleles are codominant alleles.
  - Individuals can be AB blood type.
- Human **M-N blood group**.
  - L^M/L^M (homozygote), $L^M L^N$ (heterozygote), $L^N L^N$ (homozygote).
  - Antigens present on surface of RBCs.

Gene Interactions and Modified Mendelian Ratios

- Consider **AaBb x AaBb:**
  - **Genotypes produced**:
    - 1/16 AABB
    - 2/16 AABb
    - 1/16 Aabb
    - 2/16 AaBB
    - 4/16 AaBb
    - 2/16 Aabb
    - 1/16 aaBB
    - 2/16 aaBb
    - 1/16 aabb
  - **Phenotypes Produced:**
    - 9:3:3:1 ratio
    - A_B_; A_bb; aaB_; aabb

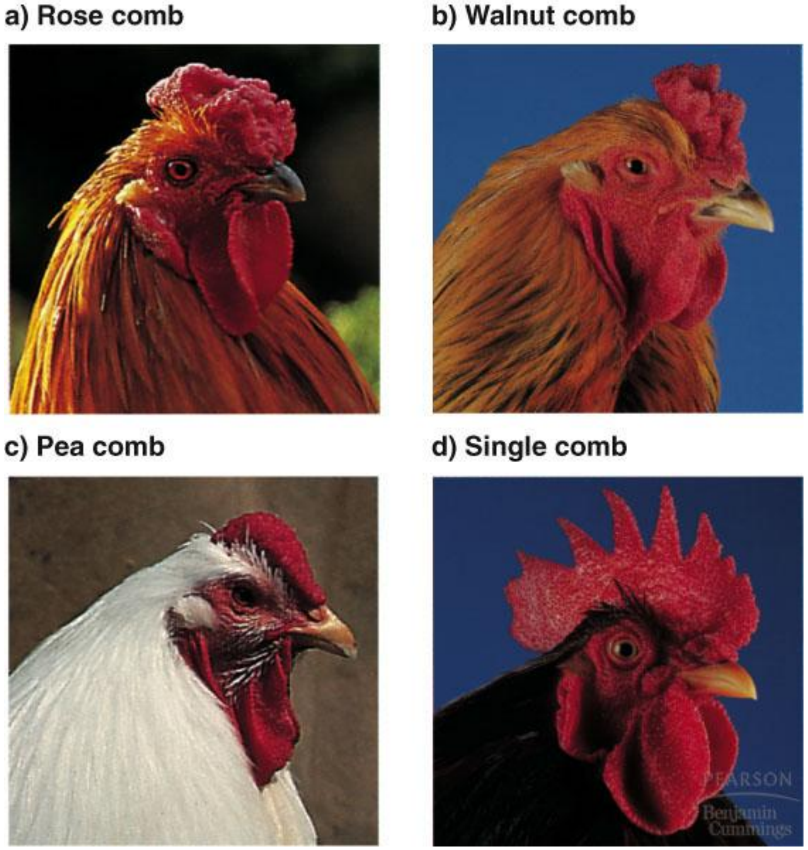
- Sometimes interactions between different genes control the same phenotype.
- Sometimes one gene can mask or modify the expression of another gene…**epistasis**.

Comb Shape in Chickens

- Comb shape in chickens is determined by the interactions of alleles of two gene loci.
- True breeding Rose x Single
  - F_1 is all rose
  - F_2 is 3 rose: 1 single
  - Rose is dominant to single
- True breeding Pea x Rose
  - F_1 is all Walnut
  - F2 is 9 Walnut: 3 Rose: 3 Pea: 1 Single

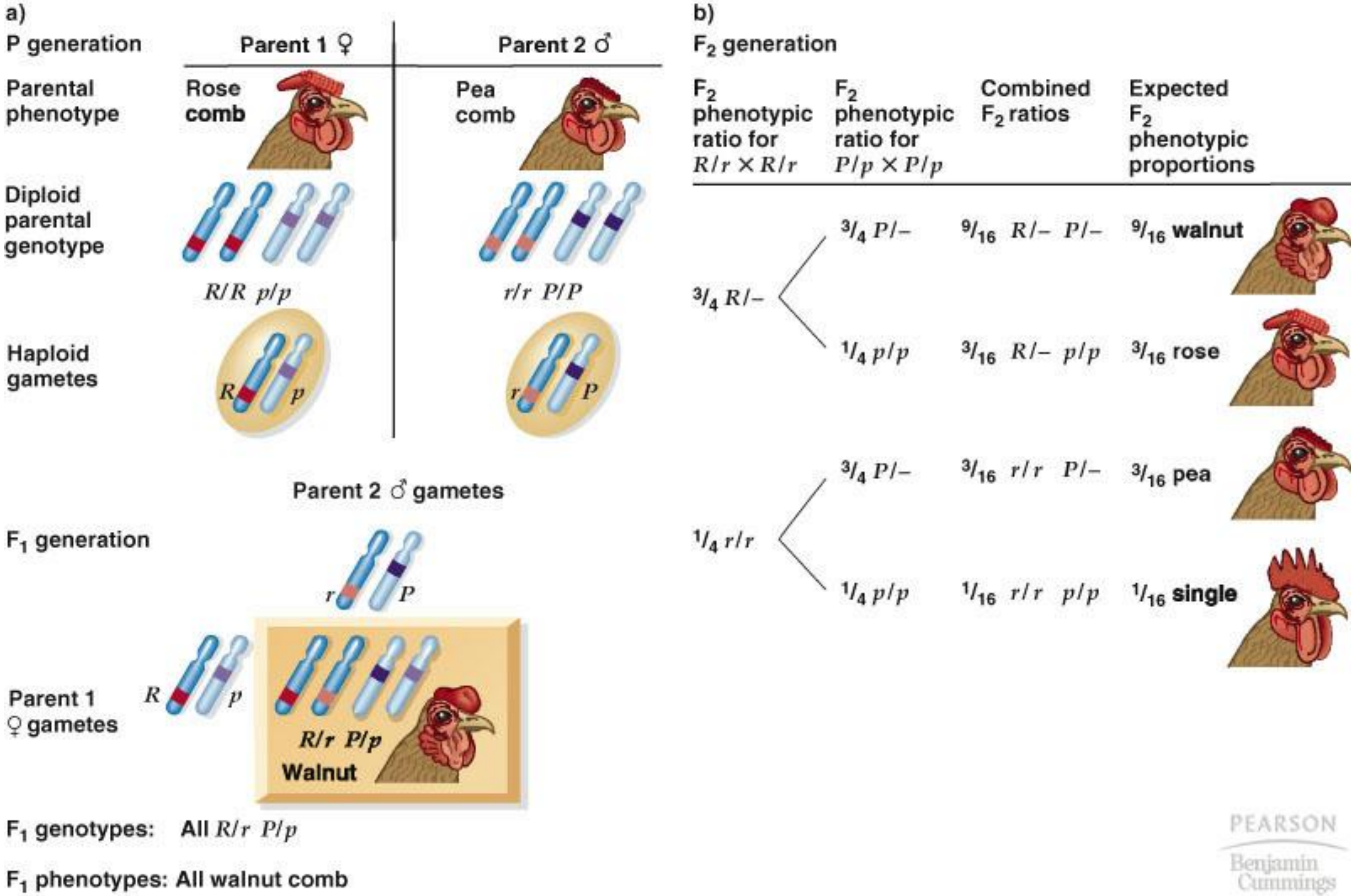
R_pp

R_P_



rrP_

rrpp



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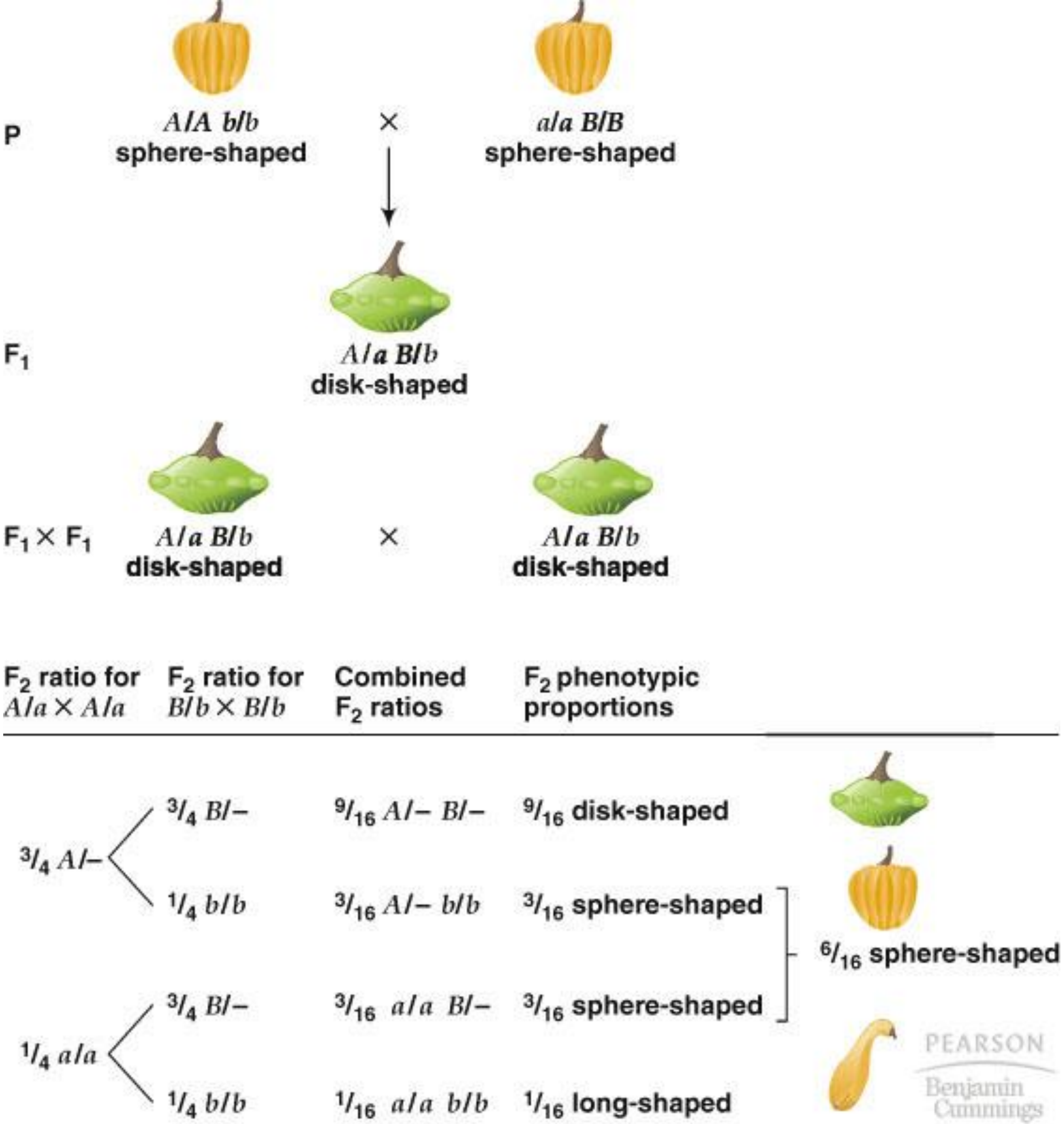
Fruit Shape in Summer Squash

- Long-fruit are always true-breeding.
- In some crosses between two different varieties of sphere-shaped plants the F_1 is disk-shaped.
  - F_2 of disk-shaped plants is:
    - 9/16 disk-shaped
    - 6/16 sphere-shaped
    - 1/16 long-shaped
- This is a modified Mendelian ratio, so two genes are likely involved.
  - A_bb or aaB_ results in sphere-shaped fruit (3+3)
  - A_B_ interact together to give disk-shaped fruit (9)
  - aabb gives the long-shaped fruit (1)



Epistasis

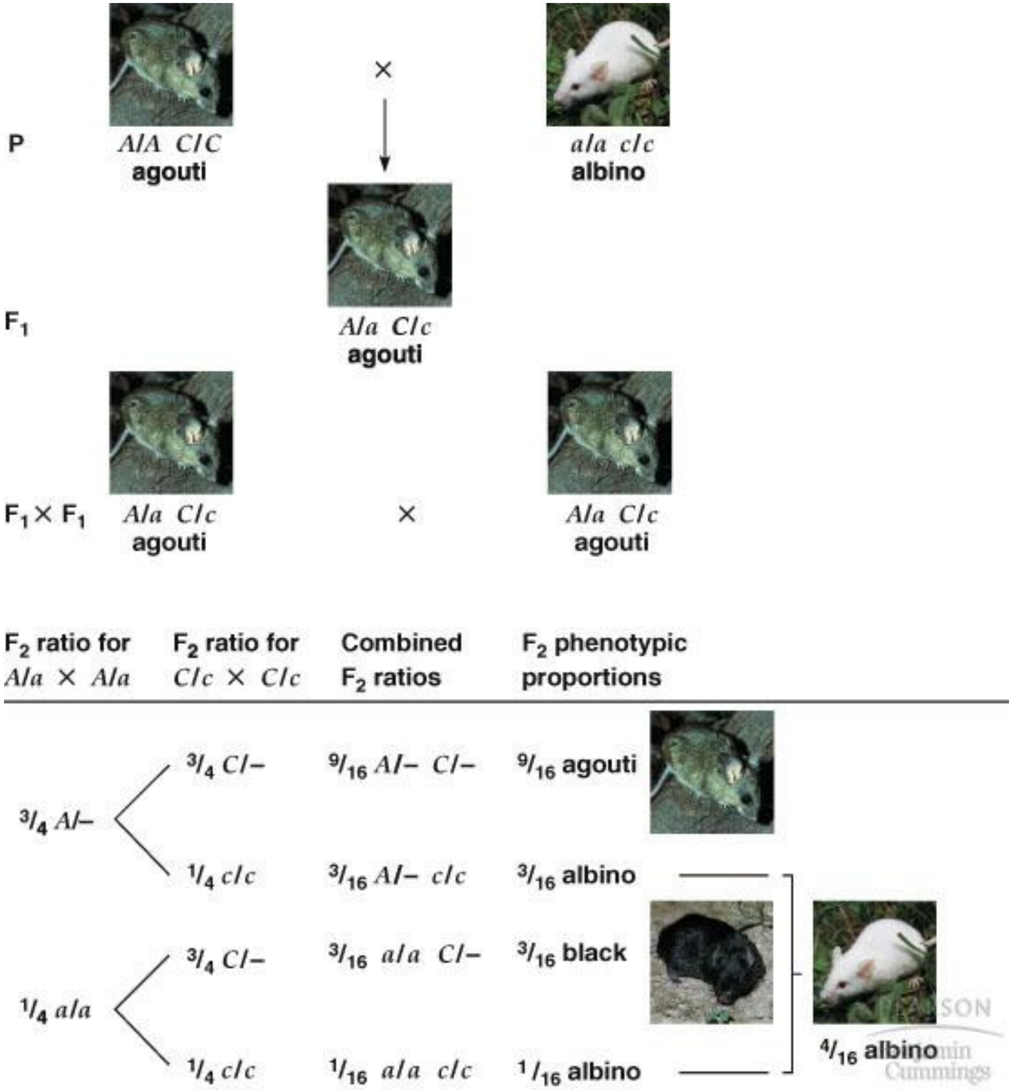
- Epistasis is the interaction between two or more genes to control a single phenotype.
  - Involves one gene masking or modifying the expression of another gene.
  - No new phenotypes are produced.
- Consider the F_2 genotypes A_B_, A_bb, aaB_ and aabb.
  - Epistasis may be caused by the presence of homozygous recessives of one gene pair which affects the expression of the other allele (**recessive epistasis**) (eg. bb affects A_)
  - Or, the A allele may mask the B allele (**dominant epistasis**)

Recessive Epistasis

- In **recessive epistasis**, A_bb and aabb individuals have the same phenotype.
  - F2 ratio is 9:3:4 instead of 9:3:3:1.
- Coat colour in mice
  - Wild mice have greyish colour produced by alternating bands of black and yellow of the hairs in their fur…called **agouti** pattern.
  - Domesticated rodents show different colours
    - **Albino** are true-breeding and have no pigment in fur and eyes.
    - **Black** mice have an absence of yellow in fur and is recessive to agouti.

Coat Colour in Mice

- Agouti x albino
  - F_1 all agouti
  - F_2 9/16 agouti, 3/16 black, 4/16 albino
- Colour in mice is determined by *C* gene.
  - C_ are black
  - cc are albino
- Agouti pattern (yellow banding) is controlled by *A* gene.
  - A_ are agouti
  - aa are nonagouti
- A_C_ agouti, aaC_ black and A_cc + aacc albino



F_2 ratio for A/a × A/a	F_2 ratio for C/c × C/c	Combined F_2 ratios	F_2 phenotypic proportions
3/4 A/–	3/4 C/–	9/16 A/– C/–	9/16 agouti
	1/4 c/c	3/16 A/– c/c	3/16 albino
1/4 a/a	3/4 C/–	3/16 a/a C/–	3/16 black
	1/4 c/c	1/16 a/a c/c	1/16 albino

Coat Colour in Labrador Retrievers

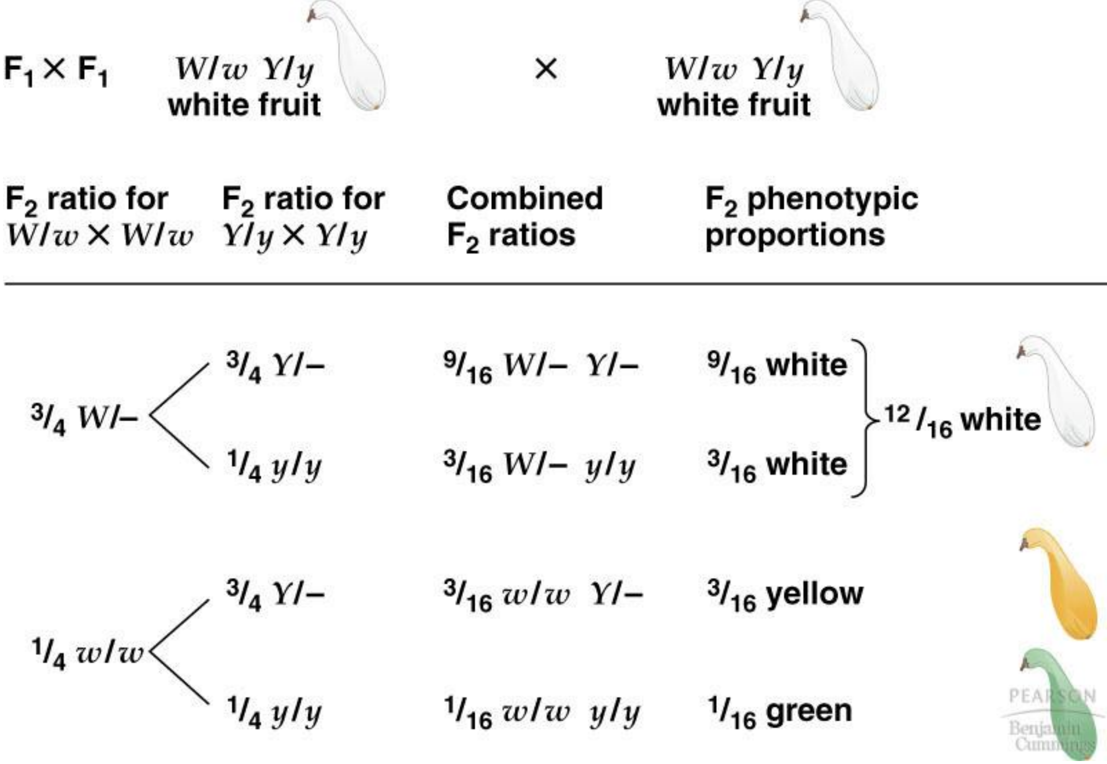
- One gene *B*_ specifies black pigment, *bb* specifies brown pigment.
- At another independent gene, *E*, allows the expression of the *B* gene, while ee does not allow expression of the *B* gene.
  - B_E_ black lab
  - bbE_ chocolate
  - -/- ee yellow lab
    - If B_ee yellow lab with dark lips and nose
    - If bbee yellow lab with pale lips and nose.

Dominant Epistasis

- In **dominant epistasis**, *A_B_* and *A_bb* individuals have the same phenotype.
  - Observe 12:3:1 ratio rather than 9:3:3:1 ratio.
  - One gene when dominant is epistatic to the other gene.
- Summer squash example:
  - Three common fruit colours: white, yellow and green.
    - White x Yellow gives White fruit
    - Yellow x Green gives Yellow fruit
      - Yellow is recessive to White, but dominant to Green.

Summer Squash: Dominant Epistasis

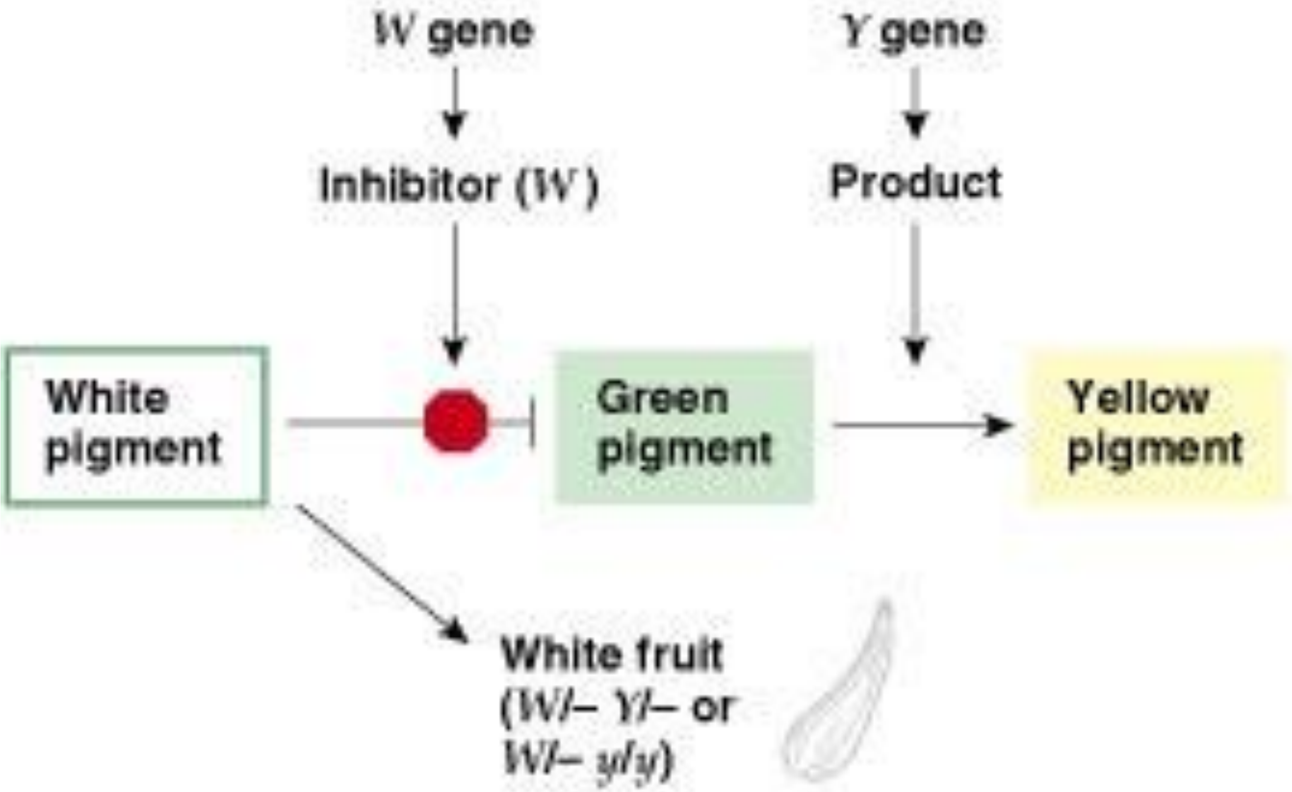
- Two gene pairs *W* and *Y*.
- *W*_ plants have white fruit regardless of other locus.
- *ww* plants will be yellow if *Y*_ or green if *yy*.



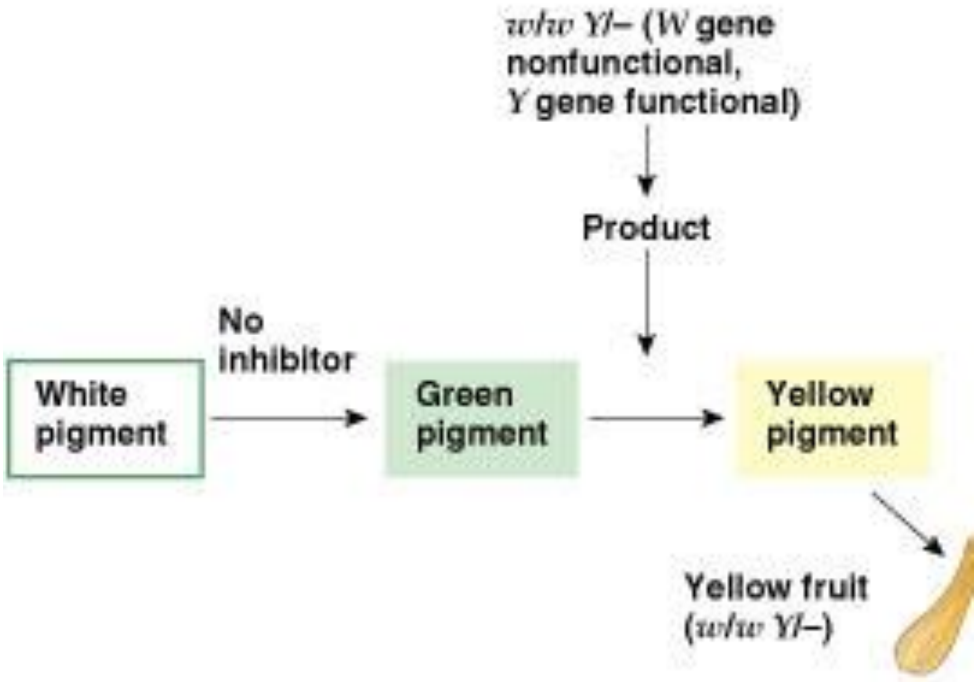
$F_1 \times F_1$ $W/w\ Y/y$ white fruit × $W/w\ Y/y$ white fruit

F_2 ratio for $W/w \times W/w$	F_2 ratio for $Y/y \times Y/y$	Combined F_2 ratios	F_2 phenotypic proportions	
$^3/_4\ W/-$	$^3/_4\ Y/-$	$^9/_{16}\ W/-\ Y/-$	$^9/_{16}$ white	$^{12}/_{16}$ white
	$^1/_4\ y/y$	$^3/_{16}\ W/-\ y/y$	$^3/_{16}$ white	
$^1/_4\ w/w$	$^3/_4\ Y/-$	$^3/_{16}\ w/w\ Y/-$	$^3/_{16}$ yellow	
	$^1/_4\ y/y$	$^1/_{16}\ w/w\ y/y$	$^1/_{16}$ green	

a) **White fruit-producing pathway**



b) Yellow fruit-producing pathway



w/w Y/– (*W* gene nonfunctional, *Y* gene functional)

Product

No inhibitor

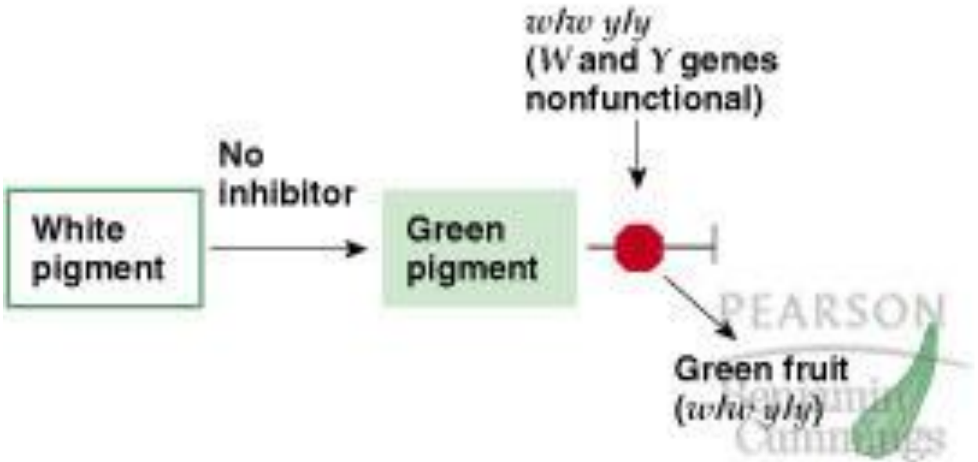
White pigment

Green pigment

Yellow pigment

Yellow fruit (*w/w Y/–*)

c) Green fruit-producing pathway



w/w y/y (*W* and *Y* genes nonfunctional)

No inhibitor

White pigment

Green pigment

Green fruit (*w/w y/y*)

Dominant Epistasis: Greying in Horses

- Horses with *GG* or *Gg* genotype will progressively grey as they age.
  - Skin and eye pigmentation remains the same, but the coat colour becomes whiter.
- *gg* horses remain the same colour throughout their life.
  - Well, they might get some greying due to old age.

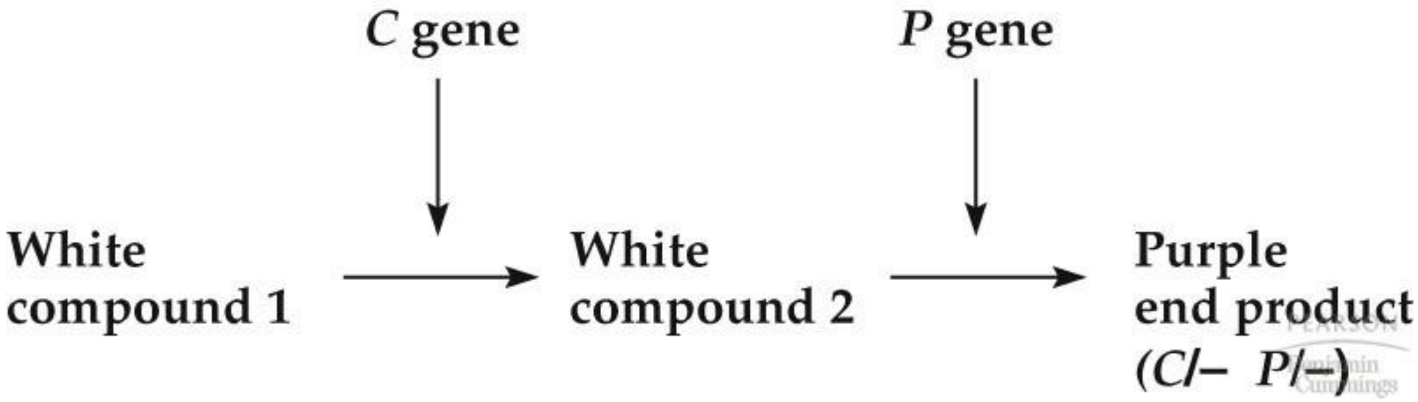
4 years

7 years

Lipizzaner

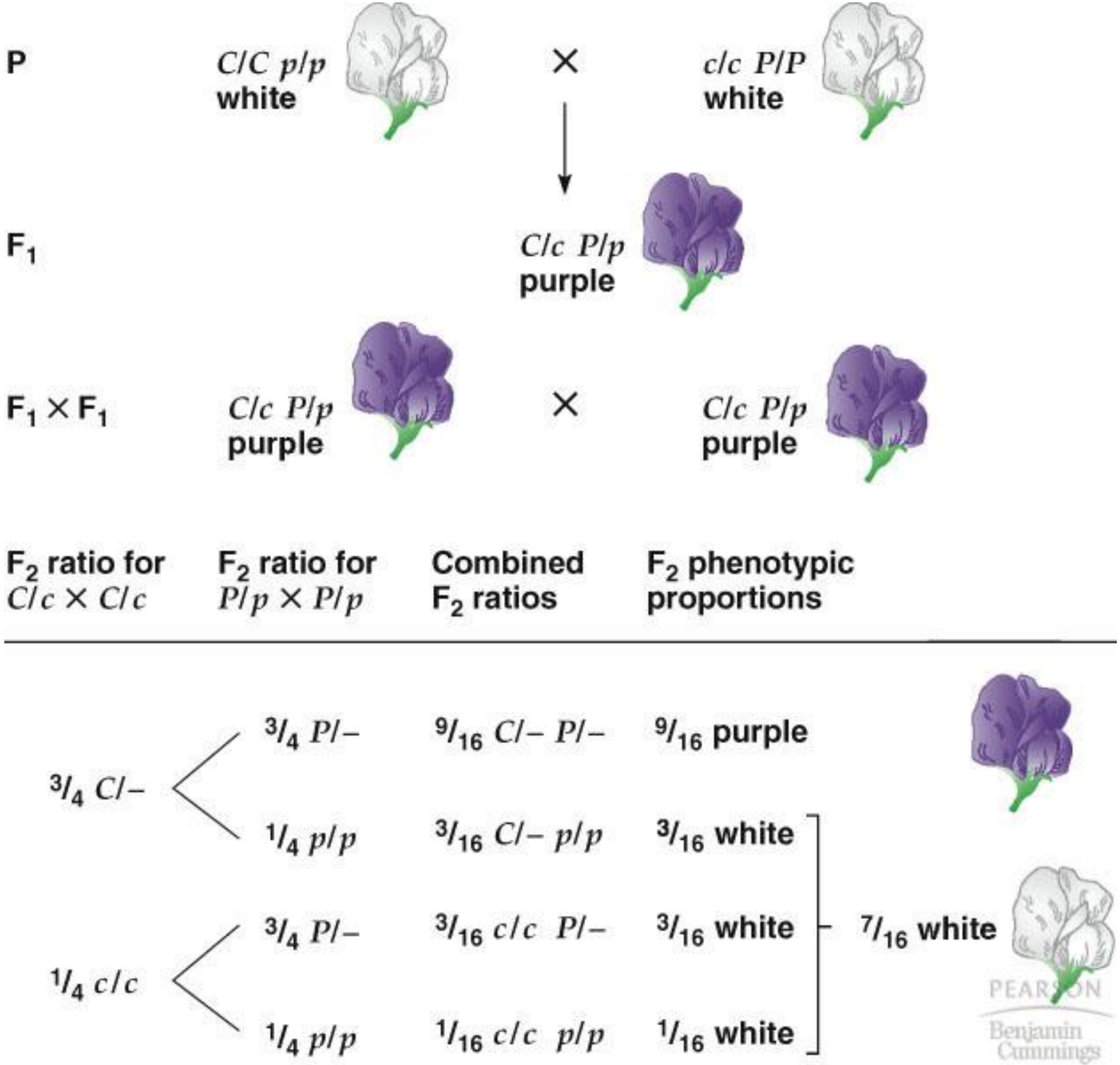
Epistasis and Duplicate Genes

- Consider the pathway below for flower colour in peas.
  - The *C* gene converts a white compound to a white intermediate and then a second gene, gene *P* converts this intermediate to a purple compound.
- *C_P_* plants are purple (9/16)
- *ccP_* and *C_pp* plants are white (7/16)
- This is the result of complementary gene action.



Epistasis and Duplicate Genes

- So in our pea plants:
  - Cross two white pea plants and the F_1 is all purple. The F_2 is 9 purple: 7 white????
  - White Parentals must have been *CCpp* x *ccPP*
    - Giving an F_1 that was *CcPp* (purple)
    - F_2 was 9 C_P_ : 7 (*ccP_* + *C_pp* + *ccpp*)


P
C/C p/p
white
×
c/c P/P
white
F1
C/c P/p
purple
F1 × F1
C/c P/p
purple
×
C/c P/p
purple
F2 ratio for C/c × C/c
F2 ratio for P/p × P/p
Combined F2 ratios
F2 phenotypic proportions
3/4 C/–
3/4 P/–
9/16 C/– P/–
9/16 purple
1/4 p/p
3/16 C/– p/p
3/16 white
1/4 c/c
3/4 P/–
3/16 c/c P/–
3/16 white
7/16 white
1/4 p/p
1/16 c/c p/p
1/16 white
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Epistasis and Duplicate Genes: Shepherd's Purse Plant

- Fruit shape in Shepherd's purse plant can either be heart shaped or narrow.
  - True-breeding heart shaped fruit plant x narrow fruit plant.
    - F_1 plants produce heart shaped fruit.
    - F_2 plants show ratio of 15 heart: 1 narrow.
    - Modification of 9:3:3:1 ratio.
      - Heart shaped *A_bb* or *aa B_* or *A_B_*
      - Narrow is *aabb*

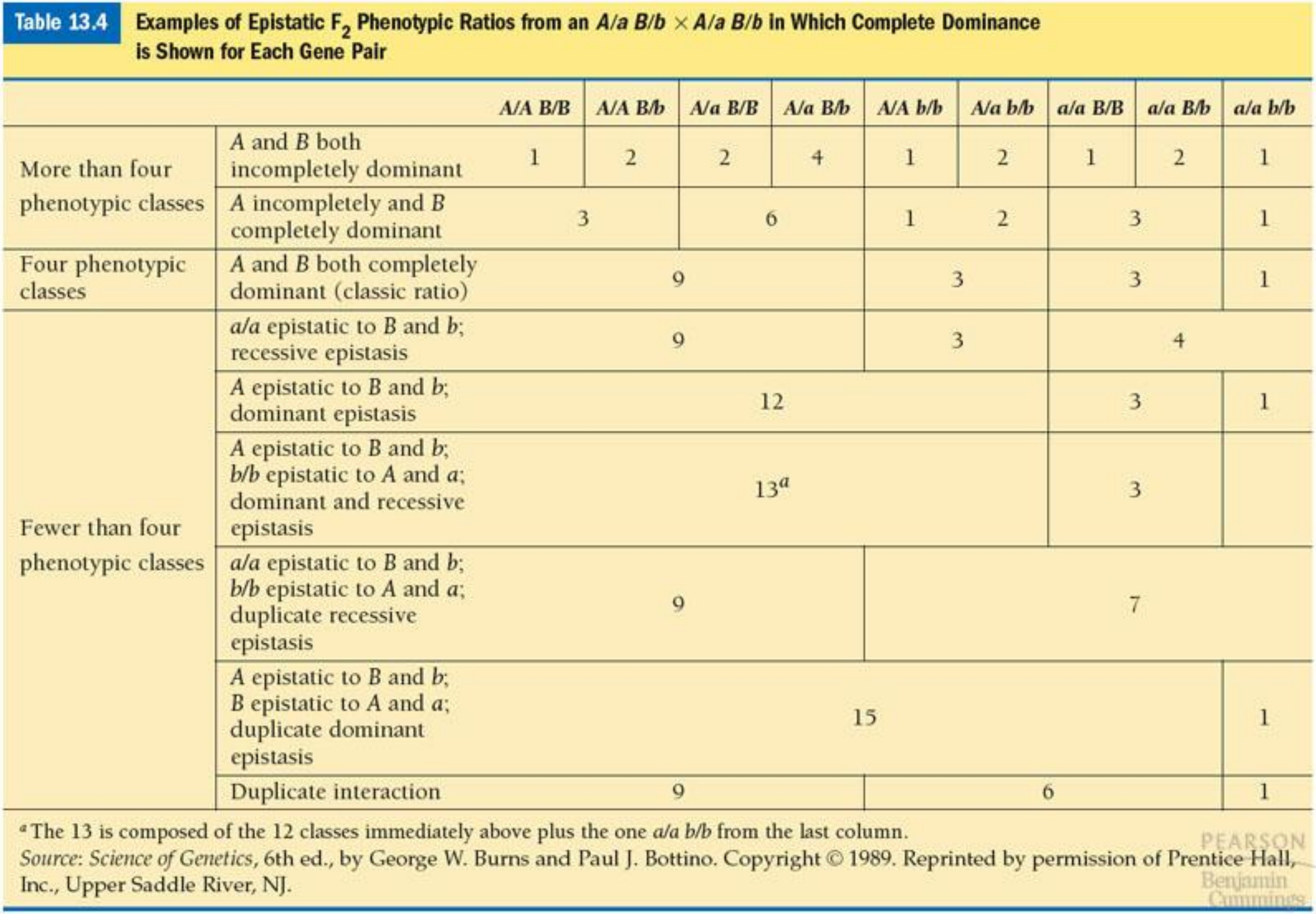


Table 13.4 **Examples of Epistatic F_2 Phenotypic Ratios from an *A/a B/b* × *A/a B/b* in Which Complete Dominance is Shown for Each Gene Pair**

<table>
<tr><th></th><th></th><th>A/A B/B</th><th>A/A B/b</th><th>A/a B/B</th><th>A/a B/b</th><th>A/A b/b</th><th>A/a b/b</th><th>a/a B/B</th><th>a/a B/b</th><th>a/a b/b</th></tr>
<tr><td rowspan="2">More than four phenotypic classes</td><td>*A* and *B* both incompletely dominant</td><td>1</td><td>2</td><td>2</td><td>4</td><td>1</td><td>2</td><td>1</td><td>2</td><td>1</td></tr>
<tr><td>*A* incompletely and *B* completely dominant</td><td colspan="2">3</td><td colspan="2">6</td><td>1</td><td>2</td><td colspan="2">3</td><td>1</td></tr>
<tr><td>Four phenotypic classes</td><td>*A* and *B* both completely dominant (classic ratio)</td><td colspan="4">9</td><td colspan="2">3</td><td colspan="2">3</td><td>1</td></tr>
<tr><td rowspan="6">Fewer than four phenotypic classes</td><td>*a/a* epistatic to *B* and *b*; recessive epistasis</td><td colspan="4">9</td><td colspan="2">3</td><td colspan="3">4</td></tr>
<tr><td>*A* epistatic to *B* and *b*; dominant epistasis</td><td colspan="6">12</td><td colspan="2">3</td><td>1</td></tr>
<tr><td>*A* epistatic to *B* and *b*; *b/b* epistatic to *A* and *a*; dominant and recessive epistasis</td><td colspan="6">13[a]</td><td colspan="2">3</td><td></td></tr>
<tr><td>*a/a* epistatic to *B* and *b*; *b/b* epistatic to *A* and *a*; duplicate recessive epistasis</td><td colspan="4">9</td><td colspan="5">7</td></tr>
<tr><td>*A* epistatic to *B* and *b*; *B* epistatic to *A* and *a*; duplicate dominant epistasis</td><td colspan="8">15</td><td>1</td></tr>
<tr><td>Duplicate interaction</td><td colspan="4">9</td><td colspan="4">6</td><td>1</td></tr>
</table>

[a] The 13 is composed of the 12 classes immediately above plus the one *a/a b/b* from the last column.

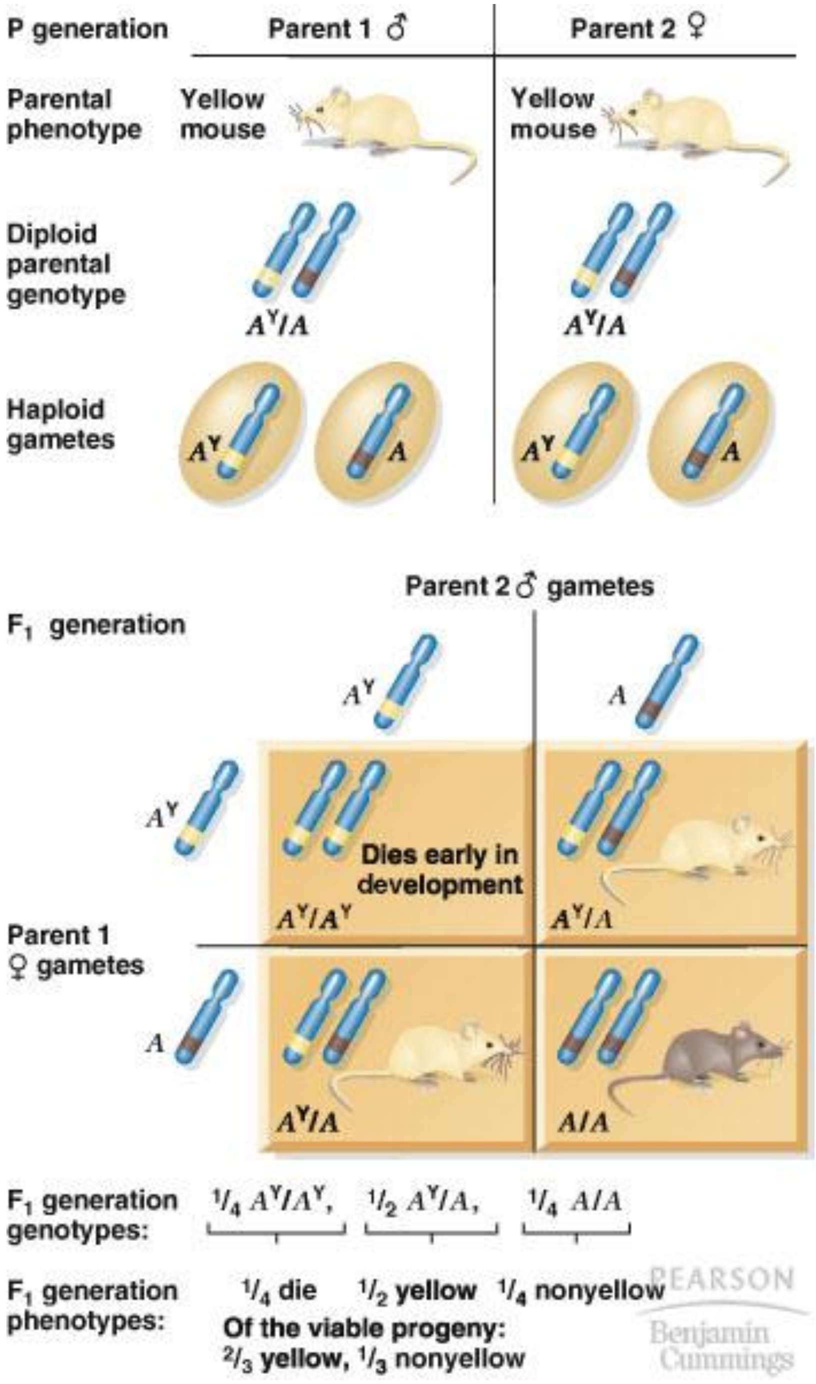
Source: *Science of Genetics*, 6th ed., by George W. Burns and Paul J. Bottino. Copyright © 1989. Reprinted by permission of Prentice Hall, Inc., Upper Saddle River, NJ.

Essential Genes and Lethal Alleles

- Mutations of genes can alter the phenotype of the organism.
- Some genes are essential for the survival of the organism, so that when mutated they cause the organism to die
  - These are called **essential genes** and the mutated form is called a **lethal allele.**
  - May be caused by a **dominant lethal allele** (both homozygous and heterozygotes die)
  - May be caused by a **recessive lethal allele** (only homozygotes die)

Yellow Body Colour in Mice

- Yellow x yellow heterozygous mice gives:
  - 800 yellow and 435 non-yellows.
  - **2:1 ratio**???
- Homozygous yellow mice die in utero.
- Yellow allele is dominant for coat colour, but acts as a **recessive lethal allele**.



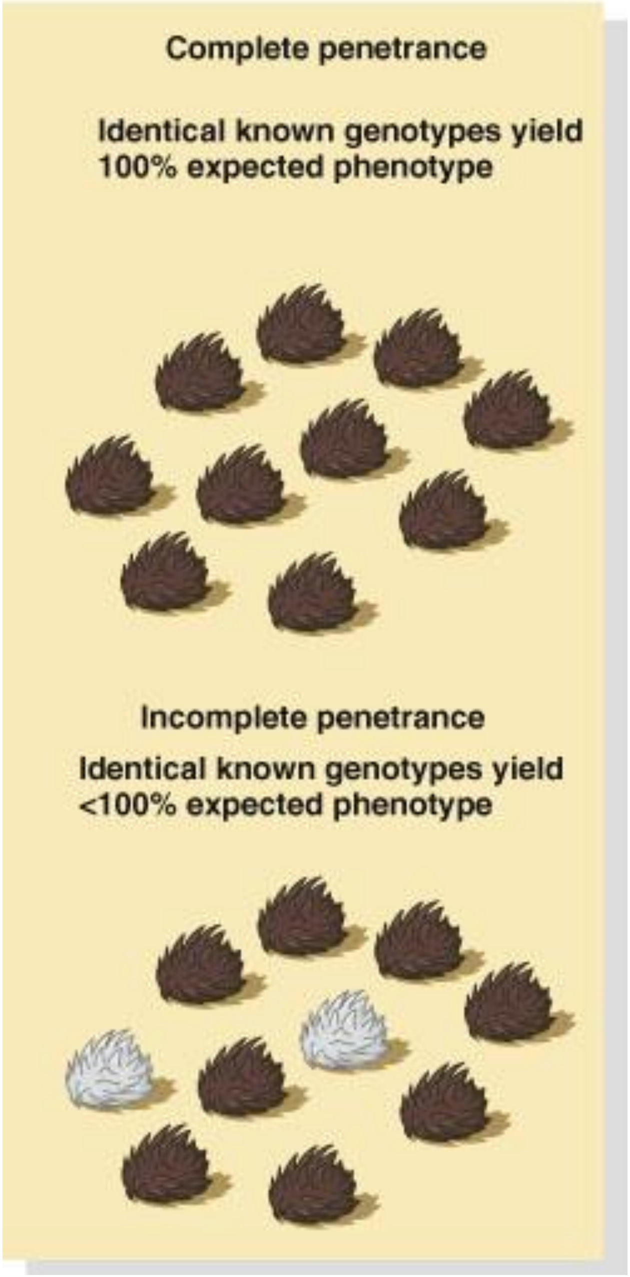
Environmental Influences: Penetrance

- Not all individuals of a certain genotype will show the expected phenotype.
  - Frequency with which a dominant or homozygous recessive gene manifests itself in individuals of a population is called **penetrance**.
  - Depends on both the **genetic background** of the individual and the **environment**.
  - If all individuals carrying a dominant allele show the mutant phenotype, then the gene shows **complete penetrance.**

Incomplete Penetrance

- **Brachydactyly** an autosomal dominant trait causing shortened and malformed fingers.
  - Shows 50 to 80 percent penetrance.
    - Only 50-80% of people with the dominant mutant allele will have the phenotype.

a)



Expressivity

- Degree to which a penetrant gene is phenotypically expressed in an individual.
- Depends on both genetic background and environment.
  - Eg. Osteogenesis imperfecta
    - Causes blueness of sclera (whites of eyes), very fragile bones and deafness.
    - Autosomal dominant disorder with 100% penetrance
    - Individuals show variable expressivity
      - Some individuals have one or more of the traits.
      - Fragility of bones may be more severe in some individuals.

a)

Complete penetrance

Identical known genotypes yield
100% expected phenotype

Incomplete penetrance

Identical known genotypes yield
<100% expected phenotype

b)

Constant expressivity

Identical known genotypes with
no expressivity effect yield
100% expected phenotype

Variable expressivity

Identical known genotypes with
an expressivity effect yield
a range of phenotypes

c)

Incomplete penetrance with variable expressivity

Identical known genotypes produce
a broad range of phenotypes,
due to varying degrees of gene
activation and expression

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Incomplete Penetrance and Variable Expressivity

- Some genes exhibit both incomplete penetrance and variable expressivity.
  - Eg. Neurofibromatosis
    - Autosomal dominant
    - Shows 50 to 80% penetrance
    - Develop tumor-like growths over entire body.
    - In milder forms causes café-au-lait spots on the skin.
    - Severe manifestations can lead to curvature of the spine, tumors of the eye and brain, high blood pressure and more…

The Effects of the Environment: Age of Onset

- Age of organism creates internal environmental changes that can affect gene function.
  - Eg. Pattern baldness appears between 20 &30 years of age.
  - Eg. Duchenne muscular dystrophy appears in children between the ages of 2 and 5 years old.
- For many disorders the nature of the age dependency is not understood.

Sex

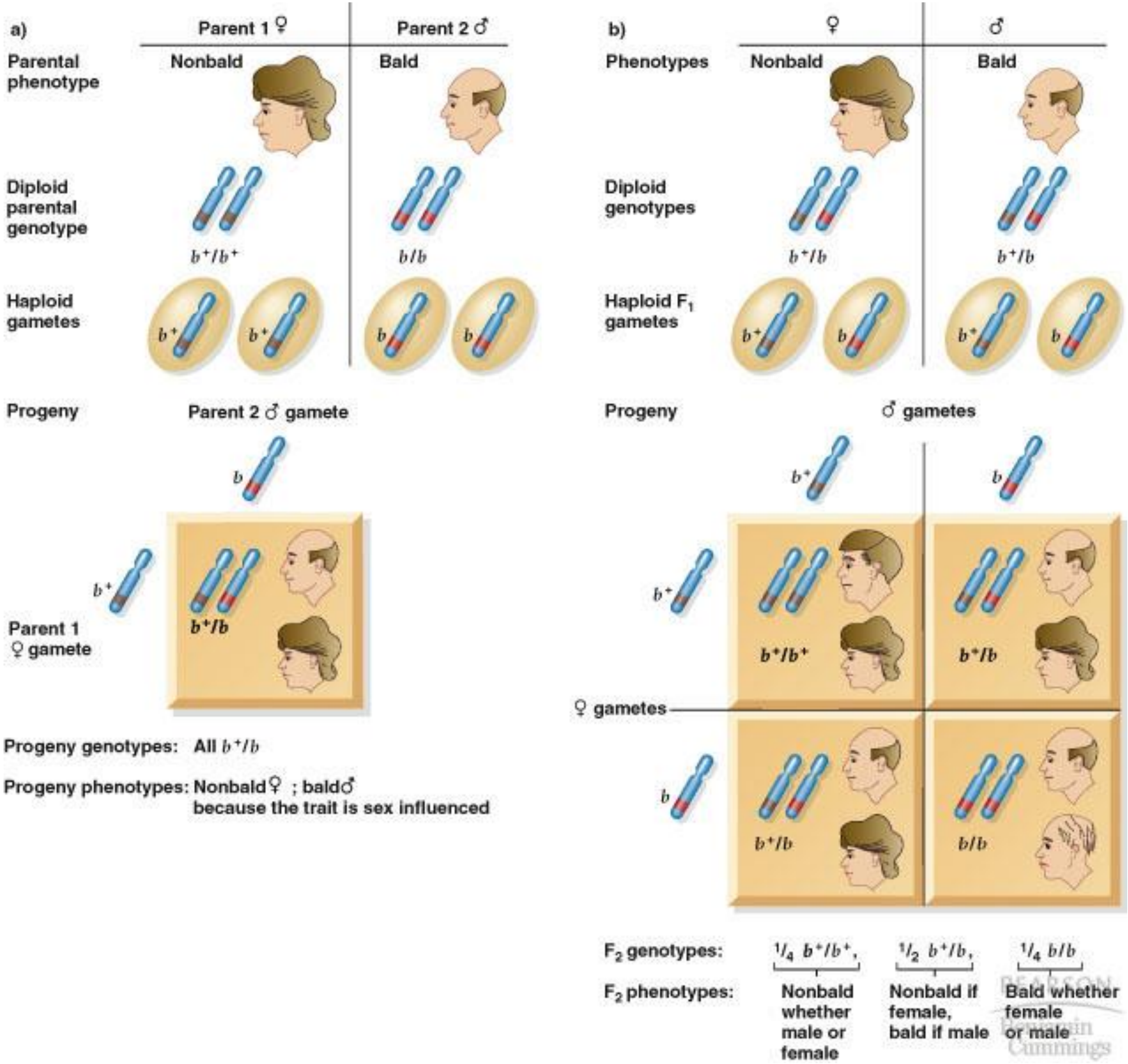
- Expression of particular genes may be influenced by the sex of the individual.
  - In the case of sex-linked genes the differences in the phenotypes between the two sexes are related to the differences in their complement of the sex chromosomes.
- Some genes that are on the autosomes affect a particular character in one sex and not the other.
  - These are called **sex-limited traits**.

Some Sex Limited Traits

- Milk production in dairy cattle.
- Horns in certain species of sheep
  - Males with genes for horns have horns, while females do not.
- Distribution of facial hair in humans.

Sex-Influenced Traits

- Often controlled by autosomal genes, such traits appear in both sexes, but either the frequency is different between the two sexes, or the relationship between the genotype and phenotype is different.
- Pattern baldness is a classic example.
  - Sex-influenced autosomal gene.
  - Dominant in males, recessive in females.
    - b^+/b^+ individuals are nonbald
    - b^+/b males are bald, females are nonbald
    - b/b individuals are bald


a)
Parent 1 ♀
Parent 2 ♂
Parental phenotype
Nonbald
Bald
Diploid parental genotype
b^+/b^+
b/b
Haploid gametes
b^+
b^+
b
b
Progeny
Parent 2 ♂ gamete
b
b^+
Parent 1 ♀ gamete
b^+/b
Progeny genotypes: All b^+/b
Progeny phenotypes: Nonbald ♀ ; bald ♂ because the trait is sex influenced
b)
♀
♂
Phenotypes
Nonbald
Bald
Diploid genotypes
b^+/b
b^+/b
Haploid F_1 gametes
b^+
b
b^+
b
Progeny
♂ gametes
b^+
b
♀ gametes
b^+
b
b^+/b^+
b^+/b
b^+/b
b/b
F_2 genotypes:
$1/4$ b^+/b^+,
$1/2$ b^+/b,
$1/4$ b/b
F_2 phenotypes:
Nonbald whether male or female
Nonbald if female, bald if male
Bald whether female or male

Pattern Baldness

- In heterozygous state b^+/b, males are bald due to the influence of the male hormone testosterone.
- Also shows variable expressivity.
  - May occur early in life or late.
  - May appear first on the crown (tonsure)
  - May appear first on forehead (receeding hairline)
  - May be complete or partial.
  - b/b females usually have late onset due to presence of female hormones.

Other Sex-Influenced Traits

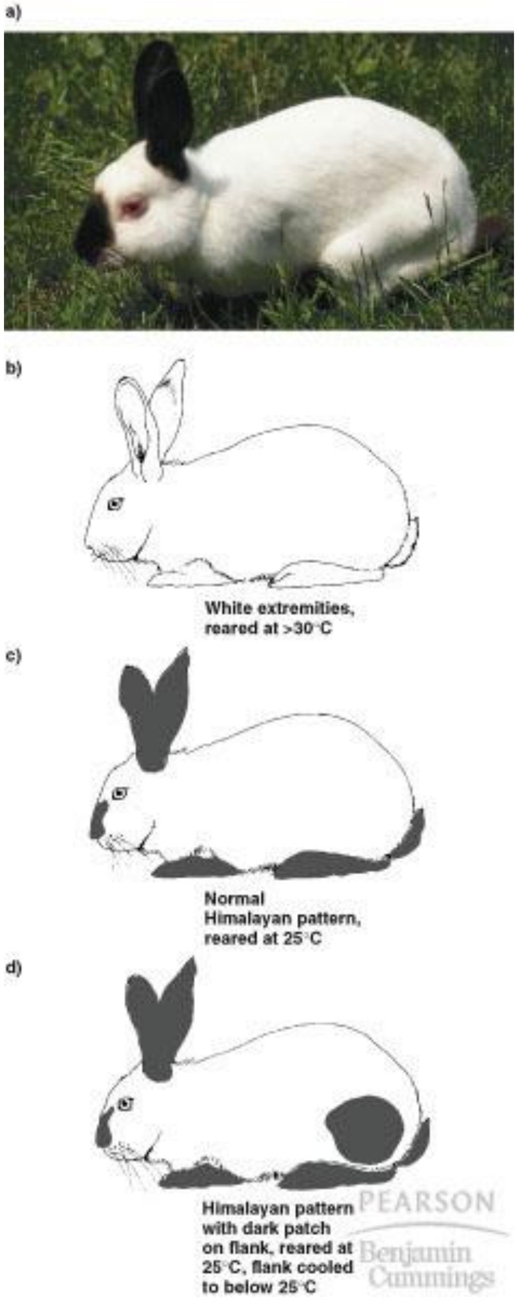
- Cleft lip/palate (2:1 male to female ratio)
- Clubfoot (2:1)
- Gout (8:1)
- Rheumatoid arthritis (1:3)
- Osteoporosis (1:3)
- Systemic lupus erythematosus (1:9)

Temperature

- Biochemical reactions are carried out by enzymes.
  - Normally these enzymes operate over a wide range of temperatures.
  - Some may be temperature sensitive.
    - May work over a certain temperature range, but not another.
- Classic example is the Himalayan rabbit and Siamese cat.

Himalayan Rabbits

- Dark fur develops in extremities
  - Ears, paws, tail and nose.
- Hypothesized that differences due to lower temperatures in these regions.
  - High body core temperature inhibits the action of a colour pigment gene to create white body colour.
- Experiments:
  - Rabbits in 30 degree incubators are white.
  - Rabbits in 25 degree incubators are Himalayan.
  - Rabbits in 25 degree incubators with cold patches develop black spots where cold patch applied.



White extremities, reared at >30°C

Normal Himalayan pattern, reared at 25°C

Himalayan pattern with dark patch on flank, reared at 25°C, flank cooled to below 25°C

Chemicals Influences

- Individuals with **Phenylketonuria** (PKU) are unable to metabolize phenylalanine.
    - Individuals homozygous recessive for this autosomal recessive allele have various symptoms.
        - Most notably mental retardation at an early age.
    - Diet determines severity of the disorder.
    - Presence of phenylalanine in food causes a build-up of the amino acid.
        - Can be treated by restricting the intake of the amino acid.

Phenocopies Induced by Chemicals

- Chemical, viral or drug exposure may produce a **phenocopy…**a non-hereditary phenotypic modification caused by environmental exposure.
  - Mimics a similar phenotype caused by a known gene mutation.
  - Genotype is normal, but phenotype is mutant.

Some Phenocopy Examples

- Mothers infected with **Rubella** (German measles) during first 12 weeks of pregnancy.
  - Child may have cataracts, deafness and heart defects….similar to effects from having rare recessive alleles.
- Mothers taking **thalidomide** (between 1959-1961) gave birth to children without the long bones of the limbs.
  - Similar to a rare dominant allele causing phocomelia.

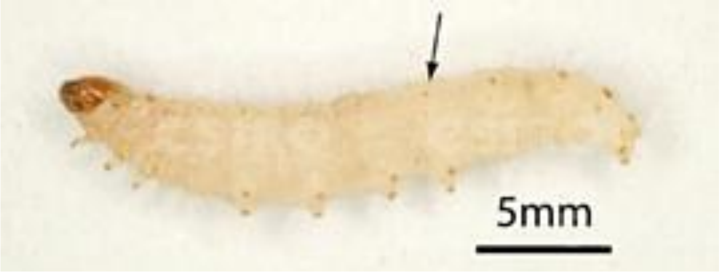
Genes and the Environment: Which one is dominant?

- Depends on the gene and the environment.
  - Sometimes environment can play a large role, while other times it plays a minor role.
  - Human height for instance relies on both.
    - The genes provide a range or potential, the environment determines the rest.
  - Alcoholism
    - Predisposition.
    - Exposure to influences.
  - IQ
    - Both genetic and environmental.

Maternal Effect

- Some maternally derived phenotypes are produced by the maternal nuclear genome (**maternal effect**), rather than inherited as extranuclear genes (**maternal inheritance**).
  - Proteins and/or mRNA deposited in the oocyte before fertilization direct early development in the embryo.
  - The genes encoding these products are on nuclear chromosomes. <u>No mtDNA is involved</u>.

Ephestia Pigmenation



- Maternal effect seen in Mediterranean meal moth, *Ephistia kuehniella*
- Pigment derived from precursor molecule kynurenine (a derivative of tryptophan)
  - Mutation “a” unable to synthesize kynurenine
  - Homozygous larva have little pigmentation and red eyes

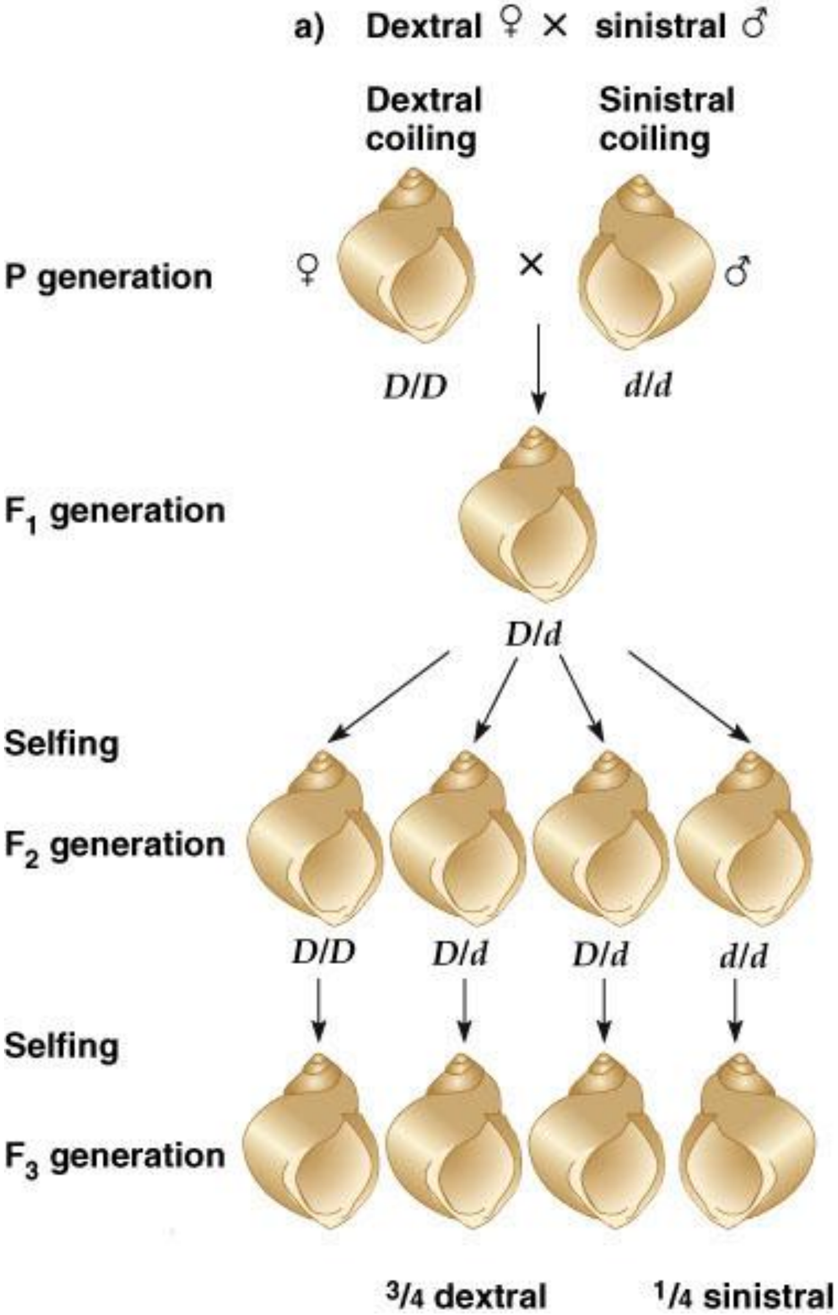
Ephistia Pigmentation

Shell Coiling in *Limnaea peregra*

- Shell coiling is determined by a pair of nuclear alleles, with the dominant *D* allele producing a dextral (right) coil, and the recessive *d* allele producing sinistral (left) coiling.
- The shell phenotype is always determined by the mother’s genotype.

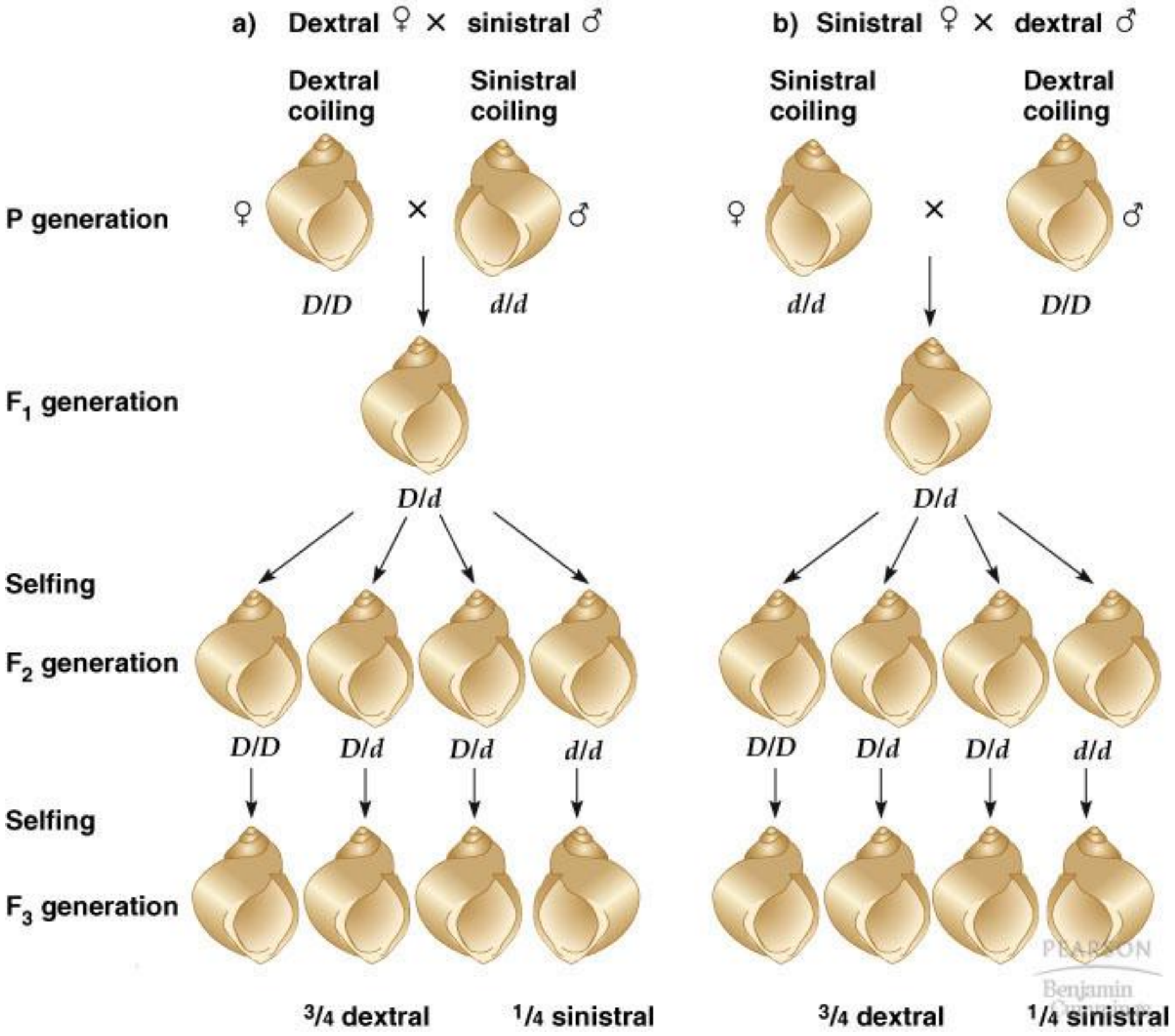
Shell Coiling in *Limnaea peregra*

- In all crosses of true-breeding dextral and sinistral snails, the F_1's have the same genotype (*D/d*) but the reciprocal crosses produce different phenotypes.
  - A dextral female (*D/D*) crossed with a sinistral male (*d/d*) produces a dextral F_1 (*D/d*)
    - The F_2 genotypes have a 1:2:1 ratio (*DD:Dd:dd*). All F_2 snails, including those with genotype d/d have dextral shells.
    - Selfing the F_2 produces an F_3 that is 3/4 dextral and 1/4 sinistral. The sinistral snails are the progeny of F_2 *d/d* mothers (who had dextral shells).


a) Dextral ♀ × sinistral ♂
Dextral coiling
Sinistral coiling
P generation
♀
×
♂
D/D
d/d
F1 generation
D/d
Selfing
F2 generation
D/D
D/d
D/d
d/d
Selfing
F3 generation
3/4 dextral
1/4 sinistral

Shell Coiling in *Limnaea peregra*

- A sinsitral female (*d/d*) crossed with a dextral male (*D/D*) produces a sinistral F_1 (*D/d*).
  - The F_2 genotypes also have a 1:2:1 ratio (*D/D : D/d : d/d*). All F_2 snails have dextral shells.
  - Selfing the F_2 produces an F_3 that is 3/4 dextral and 1/4 sinistral.


a) Dextral ♀ × sinistral ♂
Dextral coiling
Sinistral coiling
P generation
♀
×
♂
D/D
d/d
F1 generation
D/d
Selfing
F2 generation
D/D
D/d
D/d
d/d
Selfing
F3 generation
3/4 dextral
1/4 sinistral
b) Sinistral ♀ × dextral ♂
Sinistral coiling
Dextral coiling
♀
×
♂
d/d
D/D
D/d
D/D
D/d
D/d
d/d
3/4 dextral
1/4 sinistral

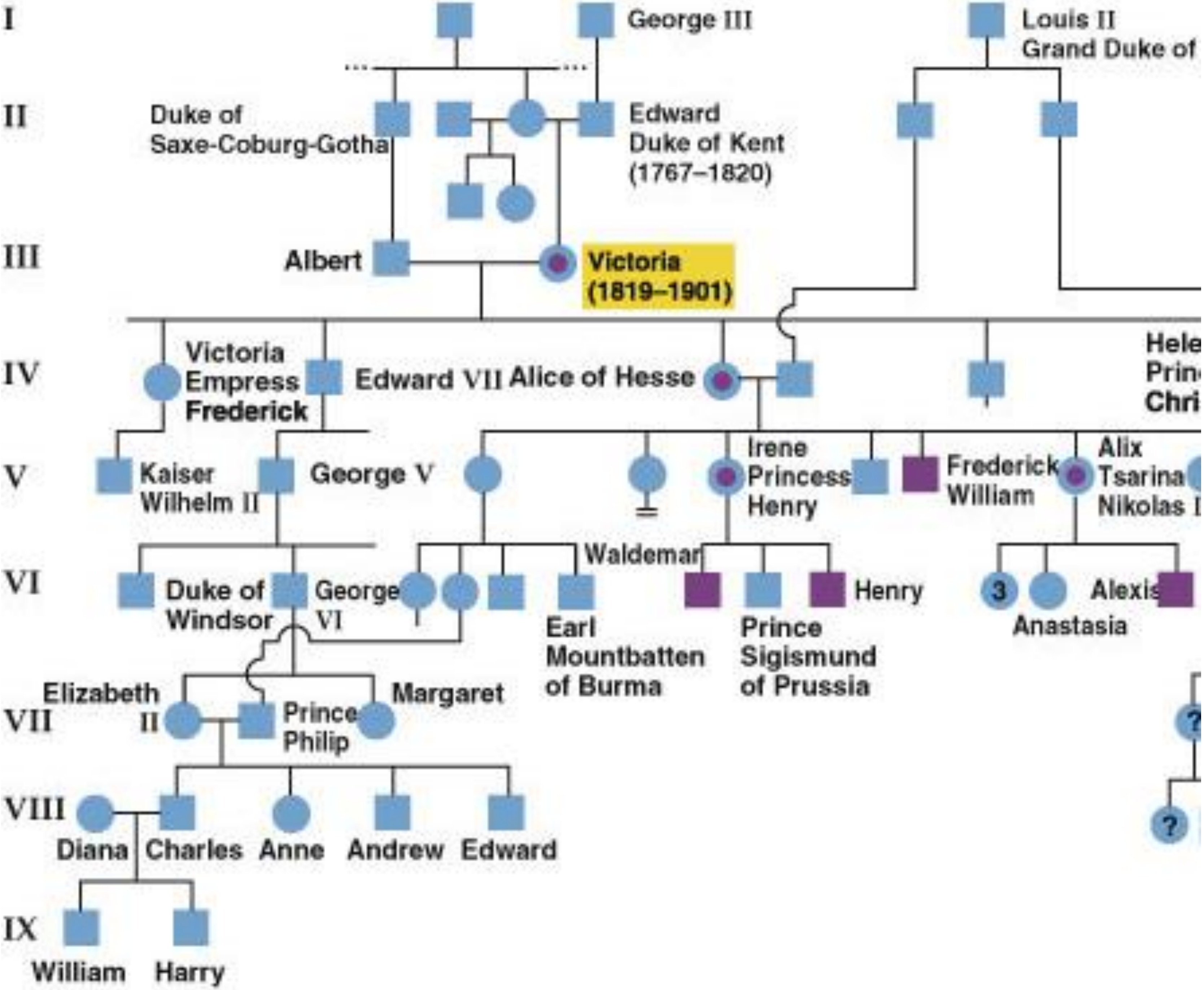
Maternal Effect

- Maternal effect is very different from extranuclear inheritance.
    - In extranuclear inheritance, the mother and progeny share a phenotype and an extranuclear genotype.
    - In maternal effect, the progeny phenotype is determined by the genotype of the mother, and not by the alleles the progeny carry.

Shell Coiling

- Direction of shell coiling is determined by the orientation of the mitotic spindle in the first mitotic division following fertilization. Maternal products within the oocyte direct orientation of the spindle, and thus shell coiling.
  - When eggs of d/d mothers are injected with cytoplasm from dextral snails, dextral progeny result.
  - When eggs of D/- mothers are injected with cytoplasm from sinistral mothers, the progeny have dextral shells.
- Interpretation is that the D allele produces a cytoplasmic product that causes dextral coiling.
  - The d allele does not produce the product, and sinistral coiling is produced by default.

The Romanovs

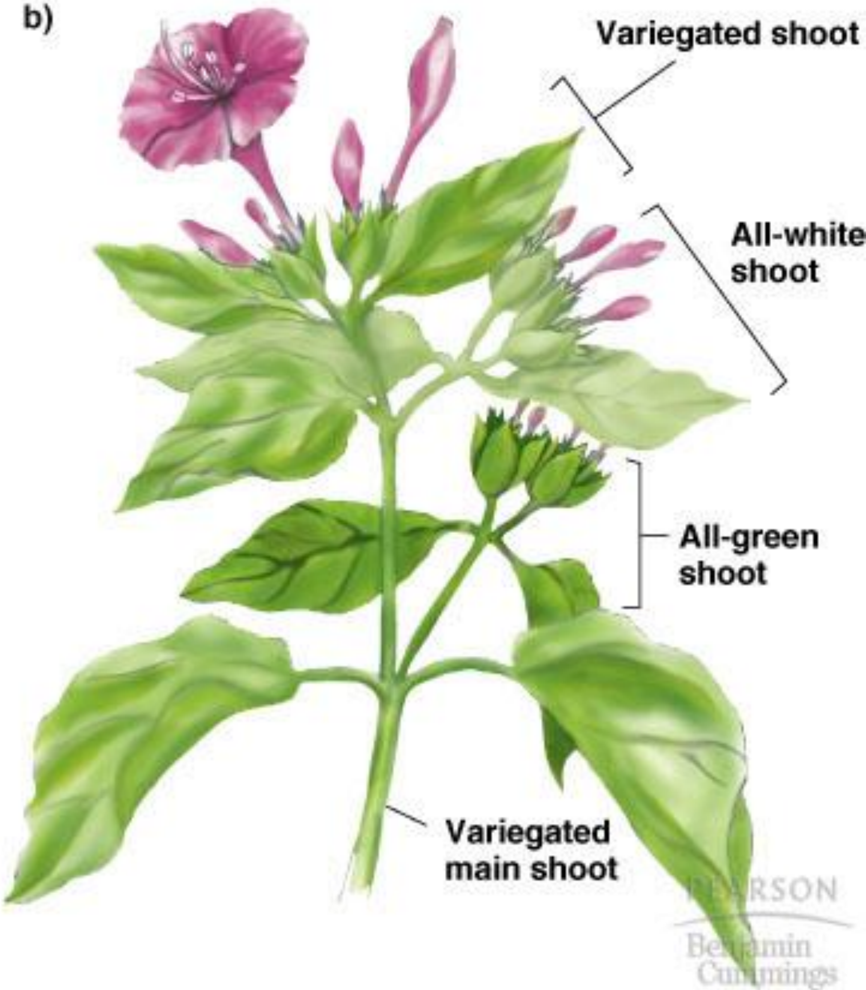

I
George III
Louis II
Grand Duke of
II
Duke of
Saxe-Coburg-Gotha
Edward
Duke of Kent
(1767–1820)
III
Albert
Victoria
(1819–1901)
IV
Victoria
Empress
Frederick
Edward VII
Alice of Hesse
Hele
Prin
Chri
V
Kaiser
Wilhelm II
George V
Irene
Princess
Henry
Frederick
William
Alix
Tsarina
Nikolas I
VI
Duke of
Windsor
George
VI
Waldemar
Henry
3
Alexis
Earl
Mountbatten
of Burma
Prince
Sigismund
of Prussia
Anastasia
VII
Elizabeth
II
Prince
Philip
Margaret
?
VIII
Diana
Charles
Anne
Andrew
Edward
?
IX
William
Harry

Examples of Non-Mendelian Inheritance

- Shoot Variegation in the Four O'Clock
  - Variegated shoot phenotype in four o'clocks involves non-Mendelian inheritance of chloroplasts in the shoots (stem, leaves and flowers).
    - Green shoots have normal chloroplasts
    - White shoots have only leucoplasts, which lack chlorophyll and are incapable of photosynthesis.
    - Variegated shoots received both chloroplasts and leucoplasts, which segregated during cell division. Progeny cells are therefore green or white, in a variegated (mixed) pattern.

a)

b)


Variegated shoot
All-white shoot
All-green shoot
Variegated main shoot

Four O’Clock Variegation

- When **ova are from green plants**, only **green** progeny result, regardless of pollen source.

- When **ova are from white plants**, only **white** progeny result (but soon die due to lack of chlorophyll), regardless of pollen source.

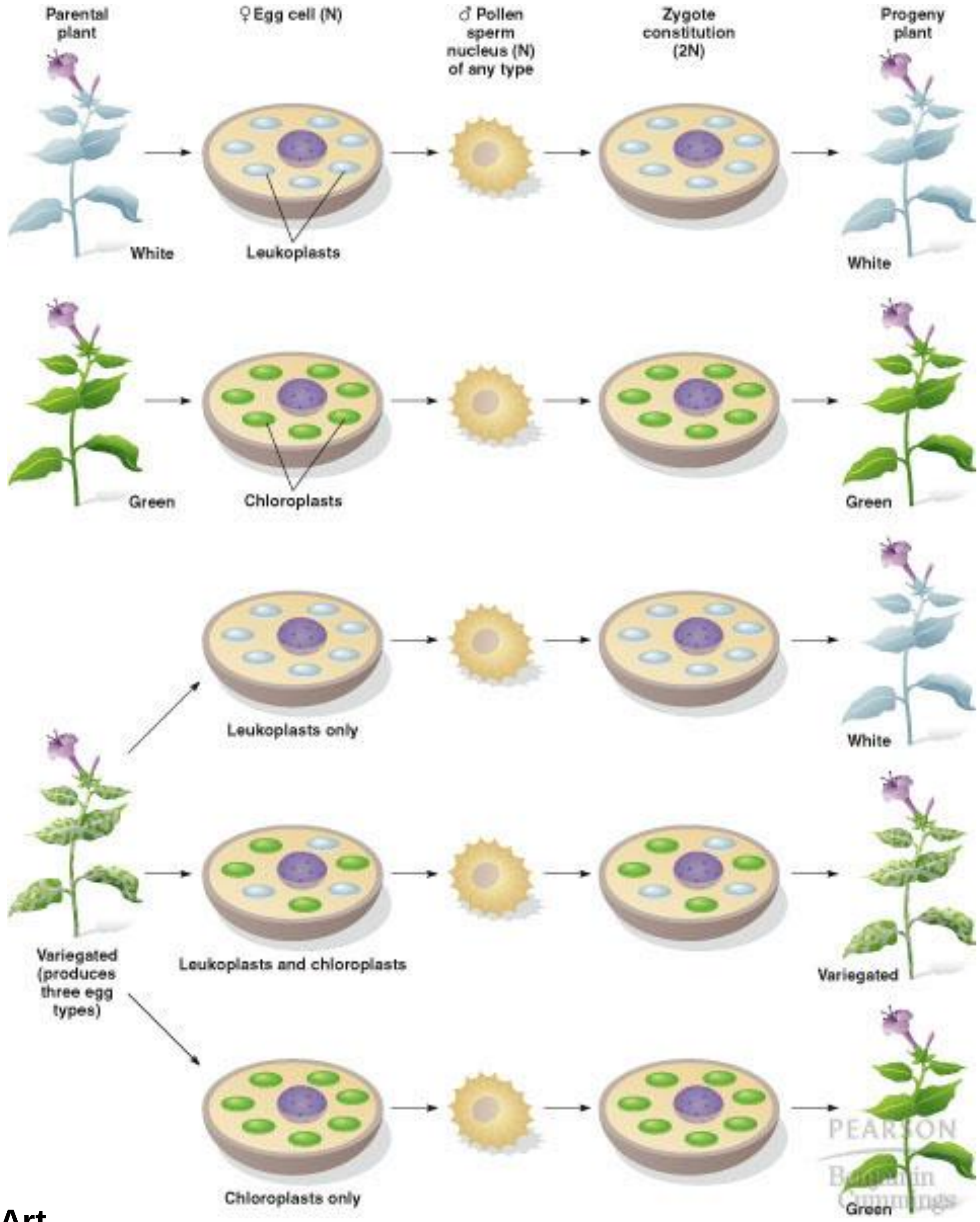
- When **ova are from variegated plants**, all **three types** of progeny result, regardless of pollen source.

Table 23.2 Results of Crosses of Variegated Plants of *Mirabilis jalapa*

Phenotype of Shoot-Bearing ♀ Parent (Egg)	Phenotype of Shoot-Bearing ♂ Parent (Pollen)	Phenotype of Progeny
White	White	White
	Green	White
	Variegated	White
Green	White	Green
	Green	Green
	Variegated	Green
Variegated	White	Variegated, green, or white
	Green	Variegated, green, or white
	Variegated	Variegated, green, or white

Four O’Clock Variegation

- Shoot colour in these plants therefore shows a pattern of maternal inheritance. There are three assumptions in the model:
  - Pollen contributes no chloroplasts or leucoplasts to the zygote.
  - The chloroplast genome replicates autonomously, so that progeny plastids retain the same colour phenotype as the original plastid.
  - Segregation of plastids during eukaryotic cell division is random, providing some offspring cells with chloroplasts, some with leucoplasts, and some with a mixture.



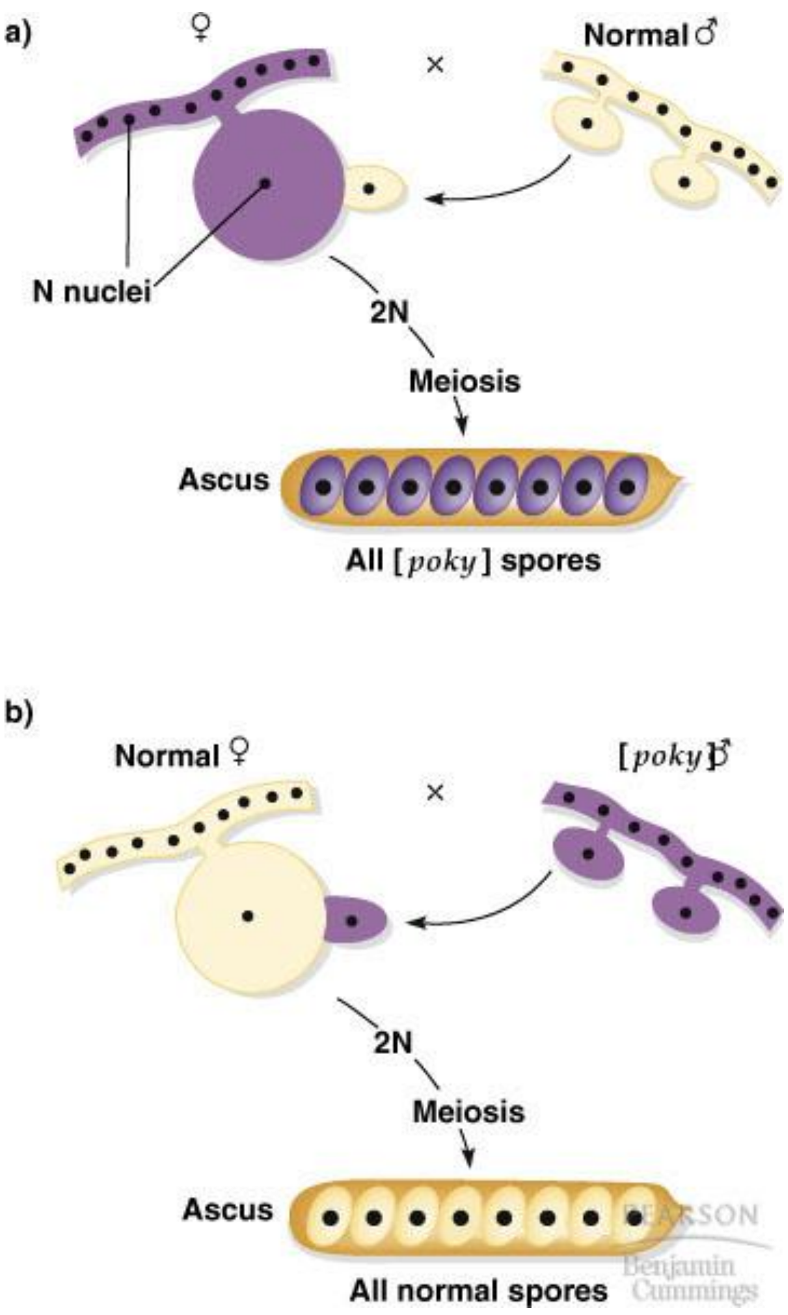
PowerPoint® Layered Art

The *poky* Mutant of *Neurospora*

- *Neurospora crassa* is an **aerobe**, and so requires mitochondrial functions to grow. The *poky* mutation in mtDNA has an altered cytochrome complement, leading to slow growth of the fungus.
- Experimental crosses in *Neurospora* involve fusion of nuclei from mating type *A* and *a* parents. Crosses can occur in two ways:
  - Place both parents on the medium at the same time.
  - Inoculate one parent onto medium, and add the second parent several days later. The first parent produces all the protoperithecia (fruiting bodies containing ascospores).

Poky

- **Protoperithecia** have much more cytoplasm than **conidia** (asexual spores).
  - The strain producing protoperithecia is similar to the female parent.
  - The second strain which contributes conidia is analogous to the male parent.
- Assigning these roles allows reciprocal crosses to be made:
  - Protoperithecia from poky parent and wt conidia results in all poky progeny.
  - Protoperithecia from wt parent and poky conidia results in all wt progeny.
  - Results indicate maternal inheritance.


a)
♀
×
Normal ♂
N nuclei
2N
Meiosis
Ascus
All [*poky*] spores
b)
Normal ♀
[*poky*] ♂
×
2N
Meiosis
Ascus
All normal spores

Poky Tetrad Analysis

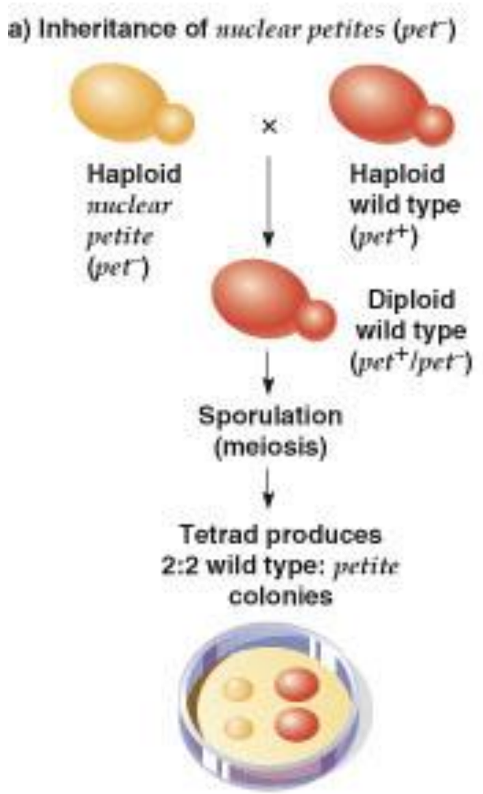
- Protoperithecia from poky parent and wt conidia results in all *poky* progeny (8:0 ratio).
- Protoperithecia from wt parent and *poky* conidia results in all wt progeny (0:8 ratio).
- In the same experiment nuclear genes segregate 4:4.

Yeast *Petite* Mutants

- Yeast can grow either **anaerobically** by fermentation (slow growth) or **aerobically** using mitochondria (fast growth) forming colonies from single cells on solid media.
- Yeast ***petite*** mutants are much smaller than those formed by wt cells, due to **cytochrome deficiencies** that prevent aerobic respiration.
  - On a medium that supports only aerobic respiration, petite cells are unable to grow.
  - The spontaneous mutation rate for this trait is 0.1-1%, but exposure to **intercalating agents** such as ethidium bromide, raises the rate to 100%.
  - This allows the production of different petite cell lines, containing different mutations.

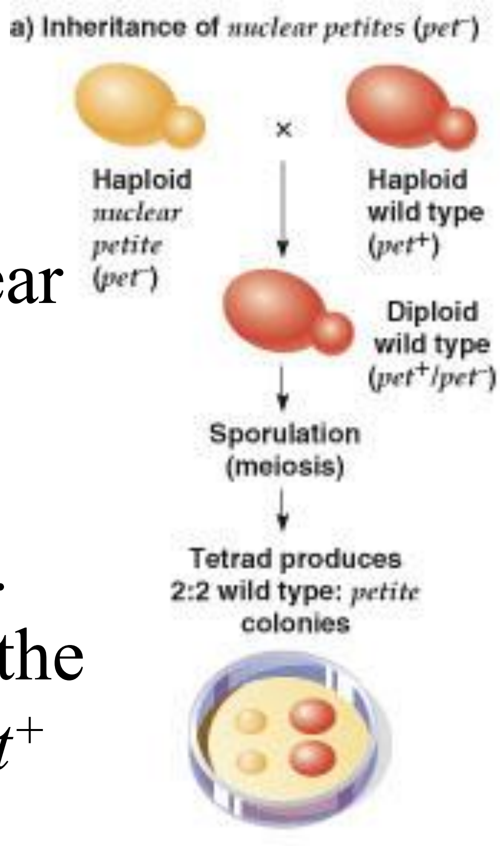
Petite Mutants

- Yeast crosses between *petite* and wt cells (**a** X α crosses) determine the mechanism of inheritance for this phenotype.
  - The zygote formed is grown into a colony to check its phenotype, and when it sporulates, the tetrad of ascospores can also be grown into colonies for phenotype analysis.



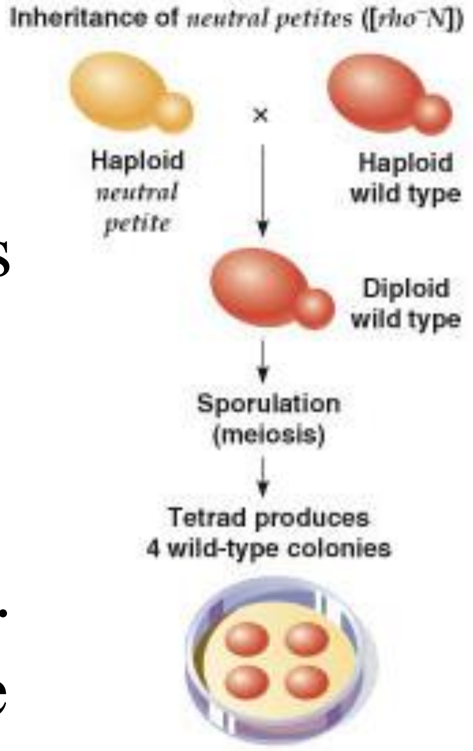
Nuclear *Petite* Mutants

- Some *petite* X wt crosses give 2:2 segregation (wt : *petite*).
  - This is the same ratio as seen in nuclear genes, so these *petite* mutants are **nuclear petites**, written *pet*$^-$.
  - The cross in this case was *pet*$^-$ X *pet*$^+$. Diploid was *pet*$^-$/*pet*$^+$ (hence wt) and the spore tetrad contained 2 *pet*$^-$ and 2 *pet*$^+$ spores.



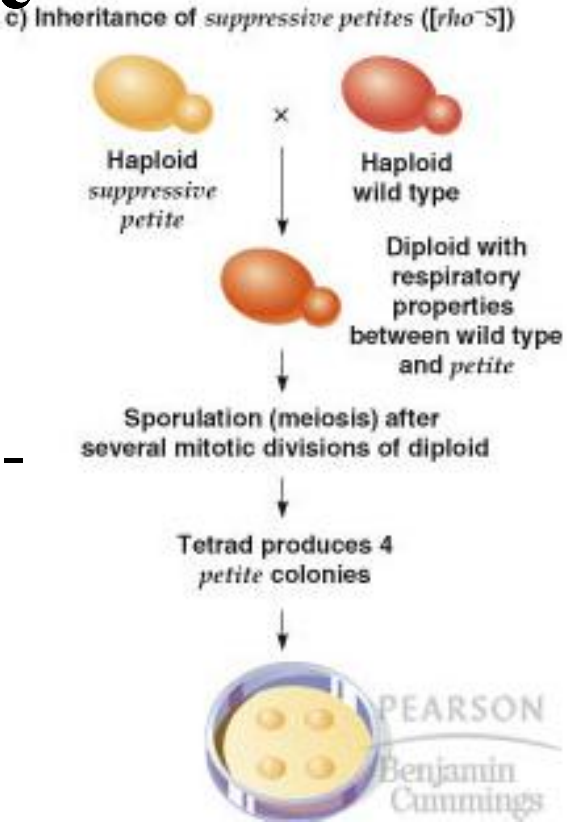
Neutral *Petites* (*rho*$^{-}$*N*)

- When crossed with wt produce wt diploids (*rho*$^{+}$*N*/*rho*$^{-}$*N*) and spores that segregate 0:4 (zero *petite* : 4 wt).
- This is an example of **uniparental inheritance** (not maternal, since gametes are same size).
- In *rho-N* mutants, nearly 100 percent of the mtDNA is missing, and so mitochondrial functions are also missing.
- Spores produce only wt colonies because normal mitochondria from the wt parent provide normal mitochondria for the progeny. The *petite* trait is lost after one generation.



Suppressive *Petites*

- Most *petite* mutants are **suppressive** (*rho*$^{-}$*S*) type. They differ from neutral petites by having an effect on the wt, although both are mutations in mtDNA.
  - A *rho*$^{+}$/*rho*$^{-}$*S* diploid has a respiratory-deficient phenotype and if it divides mitotically the progeny will nearly all be *petites*.
  - Sporulation of the *petite rho*$^{+}$/*rho*$^{-}$*S* diploid produces tetrads with a 4:0 (petite:wt) ratio.



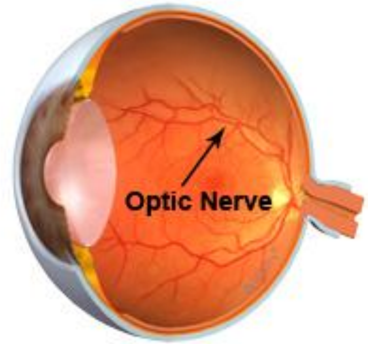
Suppressive *Petites*

- Suppressive *petites* start with deletions in mtDNA. The lost mtDNA is restored by duplications of existing mtDNA, often creating gene deletions and rearrangements that cause deficiencies in the enzymes for aerobic respiration.

- The suppressive effect over normal mitochondria might result from either:
  - Faster replication of the mutant mitochondria, outcompeting with wt, or
  - Fusion with normal mitochondria and reombination between *rho*$^-$*S* mtDNA and wt mtDNA.

Human Genetic Diseases and Mitochondrial DNA Defects

- **Leber's hereditary optic neuropathy** (LHON). Optic nerve degeneration results in complete or partial blindness in midlife adults (avg age 27).
  - LHON is caused by mutations in mtDNA genes for electron transport chain proteins.
    - 50% of cases affect NADH dehydrogenase
  - LHON results from defects in the enzymes of oxidative phosphorylation. Without ATP production, the optic nerve dies.



Human Genetic Diseases and Mitochondrial DNA Defects

- **Kearns-Sayre syndrome** produces three types of neuromuscular defects:
  - Progressive paralysis of certain eye muscles and hearing loss.
  - Abnormal pigment accumulation on the retina, causing chromic inflammation and degeneration of the retina.
  - Heart disease
  - Results from deletions in mtDNA. A model for the disorder is that tRNA genes are removed, disrupting mitochondrial translation.
  - Many KSS patients are symptom-free as children, but display progressive symptoms as adults
    - The proportion of mtDNAs with deletion mutations increases as the severity of symptoms increases

Human Genetic Diseases and Mitochondrial DNA Defects

- **Myoclonic epilepsy** and **ragged-red fibre disease**. Symptoms include:
  - Microscopic tissue abnormality, raged-red fibres.
  - Myoclonic seizures (jerking spasms).
  - Ataxia (uncoordinated movement).
  - Accumulation of lactic acid in blood.
  - Many additional symptoms…
  - Mitochondria have abnormal appearance.
  - Caused by a single nucleotide substitution in the lysine tRNA gene. Mitochondrial protein synthesis is affected, and in some way this phenotype is produced.
    - Most patients have a mixture of normal and abnormal mitochondria**---heteroplasmy**

Human Genetic Diseases and Mitochondrial DNA Defects

- In most mtDNA disorders, cells of affected individuals have a mix of normal and mutant mitochondria (**heteroplasmy**).
- Proportions of the two mitochondrial types vary between tissues, and between individuals.
- Severity of disease correlates with the relative amount of mutant mitochondria.

Exceptions to Maternal Inheritance

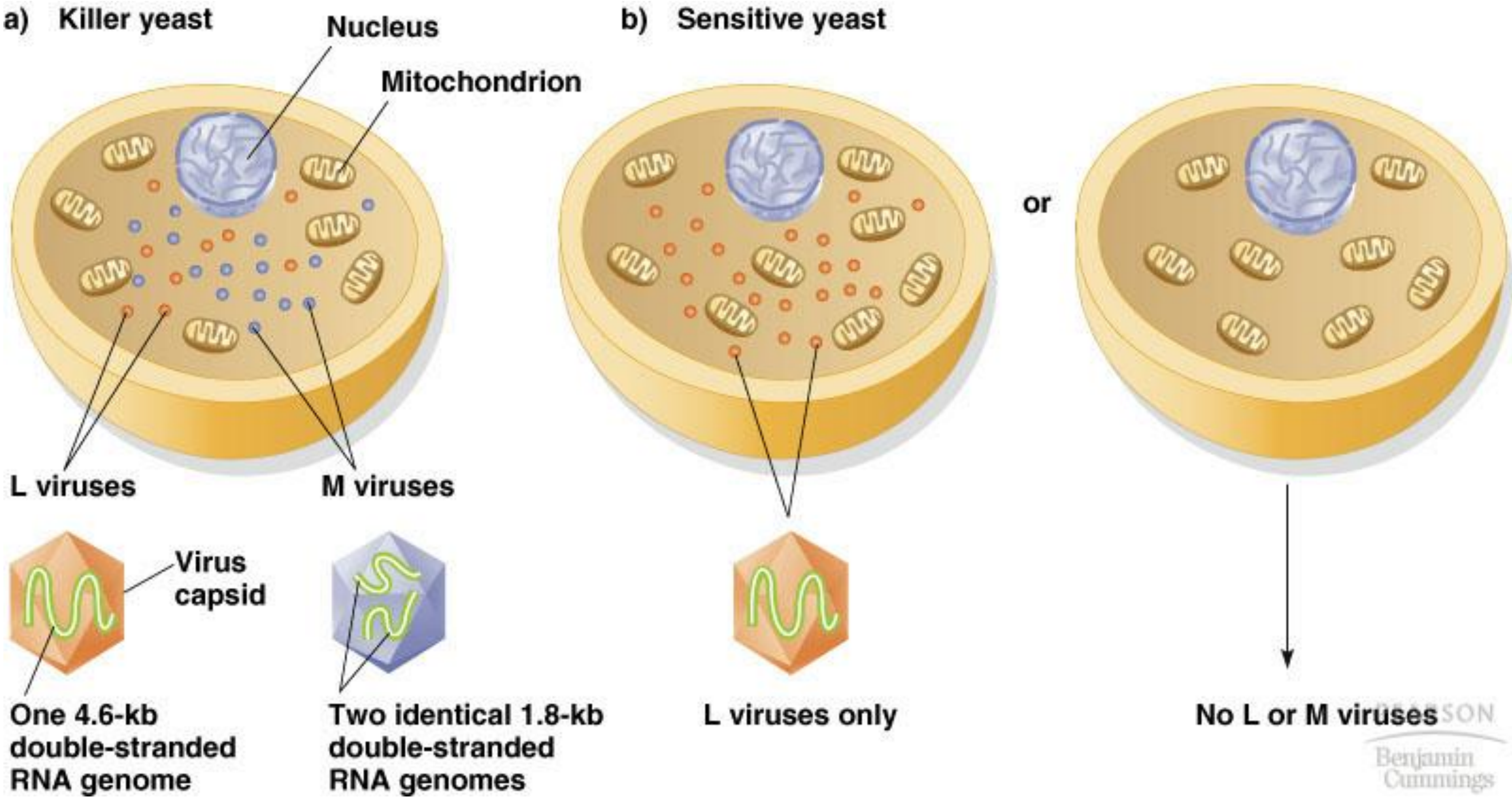
- When the female gamete contributes most of the cytoplasm, maternal inheritance is the usual explanation for extranuclear mutations. Some exceptions do occur:
  - In mice PCR shows **heteroplasmy**, with paternal mtDNA present at a frequency of 10^{-4} relative to maternal mtDNA. May facilitate recombination between mtDNAs.
  - In plants, angiosperms show variation in plastid inheritance with most inheriting only maternal plastids, but others inheriting from both parents, or from paternal parent. Paternal inheritance is also found in gymnosperms.

Infectious Heredity--Killer Yeast

- Symbiotic bacteria or viruses in eukaryotic cytoplasm may also produce extranuclear inheritance. An example is the killer phenotype in yeast:
  - Killer cells secrete a toxin that kills sensitive cells, but not killer strains.

Killer Yeast (Infectious Heredity)

- Killer phenotype results from two cytoplasmic viruses, L and M. Neither virus harms the host cell.
  - L virus is a 4.6kb dsRNA in a protein capsid. L-dsRNA encodes capsid proteins used for both viruses and viral RNA polymerase for replication.
  - M virus is found only in cells also containing L virus. M contains two copies of a 1.8kb dsRNA. M-dsRNA encodes killer toxin, which also confers immunity on the host cell.
    - Two types of cells are sensitive to the killer toxin, those with the L virus and those with neither L nor M virus.
  - Transmission of these viruses occurs during mating, with all progeny inheriting copies of the parental viruses.
  - Example of an **infectious mechanism** of cytoplasmic inheritance (infectious heredity).


a) Killer yeast
Nucleus
Mitochondrion
L viruses
M viruses
Virus capsid
One 4.6-kb double-stranded RNA genome
Two identical 1.8-kb double-stranded RNA genomes
b) Sensitive yeast
or
L viruses only
No L or M viruses