Dominance and Allelic Relationships

Complete Dominance:
- heterozygote = homozygote
- w.t. allele is *haplosufficient*

Incomplete Dominance:
- heterozygote intermediate
- w.t. allele is *haploinsufficient*
Inheritance of incompletely dominant traits follows Mendelian principles

Petal color in snapdragons:

Red $\otimes$ White

\[
\begin{align*}
RR & \quad rr \\
\downarrow & \\
F_1 & \quad \text{Pink} \quad Rr \\
\downarrow & \\
F_2 & \quad \frac{1}{4} \ \text{Red} \quad RR \\
& \quad \frac{1}{2} \ \text{Pink} \quad Rr \\
& \quad \frac{1}{4} \ \text{White} \quad rr
\end{align*}
\]
Homozygous wild types and mutants express wild type and mutant phenotypes, respectively

\[ + = \text{wild type} \]
\[ m = \text{null allele} \]

**Protein**
- **Homozygous wild type**
  - Functional
- **Heterozygote**
  - Functional
- **Homozygous mutant**
  - Nonfunctional

**mRNA**
- **Homozygous wild type**
  - Functional
- **Heterozygote**
  - Functional
- **Homozygous mutant**
  - Nonfunctional

**Chromosome**
- **Homozygous wild type**
  - +
  - +
- **Heterozygote**
  - +
  - m
- **Homozygous mutant**
  - m
  - m
Expression in heterozygotes depends on haplosufficiency

Null alleles of *haplosufficient* genes are recessive

Null alleles of *haploinsufficient* genes may lead to intermediate expression or be dominant
Haploinsufficiency

Expression depends on effect of active allele
Haploinsufficiency

Heterozygosity for a null allele:
Sled slows down = incomplete dominance
Sled stops = dominant expression of null allele

Null alleles of haploinsufficient genes may be dominant
Haploinsufficiency

Two active “wheel” alleles are necessary

Null allele (missing wheel) is expressed as dominant
Null alleles of haploinsufficient genes may be dominant

Example: regulatory proteins

Conditions for dominance:

- both wildtype alleles are necessary for *any* expression of phenotype
  - high threshold for phenotypic expression
  - no quantitative or intermediate expression

<table>
<thead>
<tr>
<th>Allele Combination</th>
<th>Haploinsufficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>+/+</td>
<td>Wildtype</td>
</tr>
<tr>
<td>M/M</td>
<td>Mutant</td>
</tr>
<tr>
<td>+/M</td>
<td>Mutant</td>
</tr>
</tbody>
</table>

2 “doses” of product

0 “dose”

1 “dose” (inadequate)

*Figure 6-3 Introduction to Genetic Analysis, Ninth Edition © 2008 W. H. Freeman and Company*
Null alleles of haploinsufficient genes may be dominant.

W.t. allele produces 5 units of an enzyme, so that:

\[ AA = 10 \text{ u}, \quad Aa = 5 \text{ u}, \quad aa = 0 \text{ u} \]

5 units necessary for w.t. phenotype (low threshold), w.t. allele is haplosufficient:

\[ AA = 10 \text{ u} = \text{wt} \quad Aa = 5 \text{ u} = \text{wt} \]

null = recessive

>5 units necessary for phenotype (high threshold), w.t. allele is haploinsufficient:

\[ AA = 10 \text{ u} = \text{wt} \quad Aa = 5 \text{ u} = \text{mut} \]

null = dominant

---

**Figure 6-3**

*Introduction to Genetic Analysis, Ninth Edition*  
© 2008 W. H. Freeman and Company
Review of Haploinsufficiency

Expressed as incomplete dominance

Expressed as dominant null allele
ABO blood types are examples of codominance -

ABO blood types are based on the presence of different genetically coded antigens on the surface of red blood cells

\[ I^A \rightarrow A \text{ antigen} \]
\[ I^B \rightarrow B \text{ antigen} \]
\[ i \rightarrow \text{no antigen} \]
Codominance in Blood Types

alleles: \( I^A = I^B > i \)

<table>
<thead>
<tr>
<th>Blood Type</th>
<th>Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>( I^A I^A ) or ( I^A i )</td>
</tr>
<tr>
<td>B</td>
<td>( I^B I^B ) or ( I^B i )</td>
</tr>
<tr>
<td>AB</td>
<td>( I^A I^B ) only</td>
</tr>
<tr>
<td>O</td>
<td>( i i ) only</td>
</tr>
</tbody>
</table>
## Match Babies with Parents

<table>
<thead>
<tr>
<th>Babies</th>
<th>Parents</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>AB x O</td>
</tr>
<tr>
<td>A</td>
<td>A x O</td>
</tr>
<tr>
<td>B</td>
<td>A x AB</td>
</tr>
<tr>
<td>AB</td>
<td>O x O</td>
</tr>
</tbody>
</table>
Codominance

Red = \(C^R C^R\)
White = \(C^W C^W\)
Hybrid = \(C^R C^W\)

Monohybrid:

\[C^R C^R \otimes C^W C^W\]

\[\downarrow\]

\(F_1\) \(C^R C^W\)

\(F_2\)

\(\frac{1}{4} C^R C^R\)
\(\frac{1}{2} C^R C^W\)
\(\frac{1}{4} C^W C^W\)

Codominant expression of petal pigment in a *Camellia*
Codominance

Red = $C^R C^R$
White = $C^W C^W$
Hybrid = $C^R C^W$

Codominant expression of petal pigment in a *Camellia*
Expression of dominance depends on how phenotype is defined, how allelic variation is expressed.

Many traits exhibit complete, incomplete and codominance.

Sickle cell anemia is one of them.
Hb alleles can be separated by electrophoresis. Hb alleles are codominant at the protein level.

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Genotype</th>
<th>Positions to which hemoglobin have migrated</th>
<th>Origin</th>
<th>Hemoglobin types present</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sickle-cell trait</td>
<td>$Hb^S/Hb^A$</td>
<td></td>
<td></td>
<td>S and A</td>
</tr>
<tr>
<td>Sickle-cell anemia</td>
<td>$Hb^S/Hb^S$</td>
<td></td>
<td></td>
<td>S</td>
</tr>
<tr>
<td>Normal</td>
<td>$Hb^A/Hb^A$</td>
<td></td>
<td></td>
<td>A</td>
</tr>
</tbody>
</table>
Expression of Dominance for Sickle Cell Anemia

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Individual</th>
<th>Red Blood Cell</th>
<th>Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>$Hb^A/Hb^A$</td>
<td>normal</td>
<td>normal</td>
<td>A only</td>
</tr>
<tr>
<td>$Hb^A/Hb^S$</td>
<td>normal</td>
<td>partial sickle</td>
<td>A and S</td>
</tr>
<tr>
<td>$Hb^S/Hb^S$</td>
<td>anemic</td>
<td>sickling</td>
<td>S only</td>
</tr>
</tbody>
</table>
Mendel’s peas showed three forms of dominance (although Mendel did not know it)

\[ W = \text{branching enzyme produces amylopectin} \]
\[ w = \text{null mutation produces amylose} \]
Amylopectin

Amylose

Wrinkled when dry

Round when dry

Starch Grains

Amylopectin

Amylopectin + Amylose

Amylose

Wrinkled when dry
Expression of Dominance for Seed Shape

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Seed</th>
<th>Starch Grains</th>
<th>Starch</th>
</tr>
</thead>
<tbody>
<tr>
<td>W/W</td>
<td>round</td>
<td>expanded</td>
<td>AP only</td>
</tr>
<tr>
<td>W/w</td>
<td>round</td>
<td>intermediate</td>
<td>AP + A</td>
</tr>
<tr>
<td>w/w</td>
<td>wrinkled</td>
<td>shrunken</td>
<td>A only</td>
</tr>
</tbody>
</table>
Dominant mutations often act as recessive lethals: homozygotes die

Pleiotropy – multiple effects from one gene
Inheritance of recessive lethals

Curly $\otimes$ Curly $\implies$ 2/3 Curly, 1/3 wildtype

Explanation: All Curly = Cy/Cy$^+$, due to homozygous (Cy/Cy) lethality:

<table>
<thead>
<tr>
<th></th>
<th>Cy</th>
<th>Cy$^+$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cy</td>
<td>Cy/Cy</td>
<td>Cy/Cy$^+$</td>
</tr>
<tr>
<td></td>
<td>dies</td>
<td>Curly</td>
</tr>
<tr>
<td>Cy$^+$</td>
<td>Cy/Cy$^+$</td>
<td>Cy$^+$/Cy$^+$</td>
</tr>
<tr>
<td></td>
<td>Curly</td>
<td>Wildtype</td>
</tr>
</tbody>
</table>

2/3 of surviving offspring are Curly
1/3 are wildtype
Other examples of pleiotropy: recessives for which a single mutation has harmful effects in different tissues

- Aboriginal New Zealanders
  - single mutation causes both sterility and respiratory difficulties
  - the mutation alters a protein required for normal function of cilia and flagella
- Northern, Central European descent - cystic fibrosis
  - poor respiration and lung disease, sterility, obstruction of small intestine
  - formation of thick mucus due to mutation in cell membrane channel protein
Multiple Alleles: A single gene may have many alleles with different phenotypes

The white eye color gene in Drosophila has different alleles that resemble each of the monogenic phenotypes shown above in a different fly species.
Different alleles of white eyes ($w$)

- different phenotypes
- may be similar to mutations in other genes

\[ w^{cf} \approx \text{sepia} \]
\[ w^{Bwx} \approx \text{brown} \]
\[ w^{c} \approx \text{vermillion} \]
Test for Allelism in Diploids – same gene or different genes?

Mutant 1 $\otimes$ Mutant 2 $\rightarrow$ F$_1$ Mutant

Mutations are allelic – same gene

$w^{cf}/w^{cf}$ $\otimes$ $w^{a}/Y$ $\rightarrow$ F$_1$ $w^{cf}/w^{a}$

“coffee” eyes $\otimes$ “apricot” eyes $\rightarrow$ F$_1$ non-wildtype

F$_1$ female carries two different mutant alleles in the same gene and is mutant
Test for Allelism in Diploids – same gene or different genes?

Mutant 1 $\otimes$ Mutant 2 $\rightarrow$ $F_1$ Wildtype

Mutations complement – different genes

$w^c/w^c; v^+/v^+$ $w^+/Y; v/v$ $w^+/w^c; v^+/v$

“crimson” eyes “vermilion” eyes wildtype

$F_1$ is heterozygous for mutations in each gene and is wildtype
Multiple Alleles in Mammalian Coat Color:

$C =$ black/brown pigment
$c^{ch} =$ chinchilla
$c^h =$ himalaya
$c =$ albino

$c^h$ - an example of conditional temperature sensitive allele
Conditional temperature sensitive effects on $c^h$
Comparison between Temperature-Sensitive Conditional, Genotype X Environment Interaction

**Temperature Sensitive**

phenotype repeatably modifiable after development complete

*ex: $sh^{ts}$, $c^h$*

**G x E Interaction**

one time effect - phenotype not modifiable after development complete
Multigene Effects and Interactions

Genes work in pathways anabolic, catabolic

Most genes affect more than one character; more than one gene affects most characters

Mutations block steps in pathways, cause mutant phenotypes
G. Beadle and E. Tatum
• studied *Neurospora* (bread mold)
  • genetics of biochemical pathways
• isolated three mutant strains
  • deficient in biochemical pathway for arginine synthesis
Microbe Nutrition and Growth

Wildtype microbes synthesize their own amino acids and vitamins if the necessary precursors are available (carbon source, inorganic salts)
  • can produce colonies on minimal medium

Microbes with nutritional mutations cannot synthesize essential nutrients
  • cannot produce colonies on minimal medium

Mutant microbes can produce colonies on medium supplemented with the missing essential nutrient
Microbial Mutant Screen

Hundreds of tubes of complete medium are inoculated with single ascospores

Mutants and wildtypes can grow

Conidia (asexual spores) from each culture are then tested on minimal medium

Only wildtypes can grow

Conidia from the cultures that fail to grow on minimal medium are then tested on a variety of supplemented media

No growth on minimal medium identifies nutritional mutant

Complete medium

Minimal medium

Minimal (control)

Minimal + amino acids

Minimal + vitamins

Complete (control)

Figure 6-11 part 2
Introduction to Genetic Analysis, Ninth Edition
© 2008 W.H. Freeman and Company
G. Beadle and E. Tatum
Isolated three mutations
• blocked synthesis of the amino acid argenine
• were nonallelic – assorted independently
B & T tested growth (+/-) on different potential intermediates in the argenine synthesis pathway
• discovered differences between the mutants
Potential intermediates in the arginine synthesis pathway

Ornithine  
\[
\text{NH}_2 \quad \text{NH} \quad \text{NH}
\]
\[
\text{(CH}_2\text{)}_3 \quad \text{(CH}_2\text{)}_3 \quad \text{(CH}_2\text{)}_3
\]
\[
\text{CHNH}_2 \quad \text{CHNH}_2 \quad \text{CHNH}_2
\]
\[
\text{COOH} \quad \text{COOH} \quad \text{COOH}
\]

Citrulline  
\[
\text{NH}_2 \quad \text{NH} \quad \text{NH}
\]
\[
\text{(CH}_2\text{)}_3 \quad \text{(CH}_2\text{)}_3 \quad \text{(CH}_2\text{)}_3
\]
\[
\text{CHNH}_2 \quad \text{CHNH}_2 \quad \text{CHNH}_2
\]
\[
\text{COOH} \quad \text{COOH} \quad \text{COOH}
\]

Arginine
Each mutant grew on a different combination of supplements

**Table 6-1** Growth of *arg* Mutants in Response to Supplements

<table>
<thead>
<tr>
<th>Mutant</th>
<th>Ornithine</th>
<th>Citrulline</th>
<th>Arginine</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>arg</em>-1</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><em>arg</em>-2</td>
<td>−</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><em>arg</em>-3</td>
<td>−</td>
<td>−</td>
<td>+</td>
</tr>
</tbody>
</table>

**Note:** A plus sign means growth; a minus sign means no growth.
# Beadle and Tatum’s Interpretation

<table>
<thead>
<tr>
<th>Mutant</th>
<th>Ornithine</th>
<th>Citrulline</th>
<th>Arginine</th>
</tr>
</thead>
<tbody>
<tr>
<td>arg-1</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>arg-2</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>arg-3</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

**Precursor** → **Orn** → **Cit** → **Arg**

- **Ornithine**
  - $\text{NH}_2$
  - $(\text{CH}_2)_3$
  - $\text{CHNH}_2$
  - COOH

- **Citrulline**
  - $\text{NH}_2$
  - $\text{C}=\text{O}$
  - $\text{NH}$
  - $(\text{CH}_2)_3$
  - $\text{CHNH}_2$
  - COOH

- **Arginine**
  - $\text{NH}_2$
  - $\text{C}=\text{NH}$
  - $\text{NH}$
  - $(\text{CH}_2)_3$
  - $\text{CHNH}_2$
  - COOH
Biochemical Pathways: a general model

Precursor (upstream end)

enzyme A ⟷ gene $a^+$ (or A)

Intermediate

enzyme B ⟷ gene $b^+$ (or B)

Product (downstream end)
Biochemical pathways usually have many steps

Precursor

Intermediate 1

Intermediate 2

Intermediate 3

Intermediate 4

Product

enzyme A $\leftrightarrow$ gene $a^+$

enzyme B $\leftrightarrow$ gene $b^+$

enzyme C $\leftrightarrow$ gene $c^+$

enzyme D $\leftrightarrow$ gene $d^+$

enzyme E $\leftrightarrow$ gene $e^+$
Tryptophan synthesis in prokaryotes:
An example of a multistep biochemical pathway controlled by different genes

Figure 11-21
*Introduction to Genetic Analysis*, Tenth Edition
© 2012 W. H. Freeman and Company
Genetic analysis of biochemical pathways in microbes and prokaryotes

Five different groups of mutants were isolated. Their growth patterns on different supplements (intermediates) are shown below:

<table>
<thead>
<tr>
<th>Mutant</th>
<th>Sup A</th>
<th>Sup B</th>
<th>Sup C</th>
<th>Sup D</th>
<th>Sup E</th>
<th>Sup F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grp 1</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Grp 2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Grp 3</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Grp 4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Grp 5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

Determine the order of the intermediates in the biochemical pathway and the mutant that controls each step:

B → C → A → E → D → F

B: 3  C: 1  A: 4  E: 2  D: 5  F
Test for Allelism in Diploids and Basis for Gene Interaction

Mutant 1 $\otimes$ Mutant 2 $\rightarrow$ $F_1 = $ Mutant
Mutations are allelic – same gene

Mutant 1 $\otimes$ Mutant 2 $\rightarrow$ $F_1 = $ Wildtype
Mutations are in different genes

In each case, mutant 1 and mutant 2 may have the same or different phenotypes

- If mutant 1 and mutant 2 are in different genes and affect the same character
- Then they may interact to produce a modified 9:3:3:1 ratio in the $F_2$
Mutations are in the same gene

Mutations are in different genes affecting the same character - Interaction modifies 9:3:3:1 ratio

Figure 6-15 part 1
*Introduction to Genetic Analysis, Ninth Edition*
© 2008 W.H. Freeman and Company
Figure 6-15 part 2

Introduction to Genetic Analysis, Ninth Edition
© 2008 W.H. Freeman and Company
A biochemical pathway for complementary protein coding genes

**Mutant "£"**
- w1 gene
- w2 gene

**Mutant "¥"**
- w1 gene
- w2 gene

White £ × White ¥

**Complementation**
- £ + ¥

**Enzyme 1**
- White £
- Enzyme 2
- White ¥
**Generalized Biochemical Pathway:** petal pigmentation as an example

**Precursor:** no pigment = white

**Intermediate:** no pigment = white

**Product:** blue pigment
Generalized Biochemical Pathway: effects of mutations

**Precursor:** no pigment = white

<table>
<thead>
<tr>
<th>Precursor</th>
<th>no pigment</th>
<th>=</th>
<th>white</th>
</tr>
</thead>
<tbody>
<tr>
<td>enzyme A</td>
<td>gene a</td>
<td></td>
<td>mutant = white</td>
</tr>
</tbody>
</table>

**Intermediate:** no pigment = white

<table>
<thead>
<tr>
<th>Intermediate</th>
<th>no pigment</th>
<th>=</th>
<th>white</th>
</tr>
</thead>
<tbody>
<tr>
<td>enzyme B</td>
<td>gene $b^+$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Phenotype:** white
Generalized Biochemical Pathway: effects of mutations

**Precursor:** no pigment = white

enzyme A \[\rightarrow\] gene \(a^+\)

**Intermediate:** no pigment = white

enzyme B \[\rightarrow\] gene \(b\) mutant = white

**Phenotype:** white
Generalized Biochemical Pathway: effects of mutations

**Precursor:** no pigment = white

**Intermediate:** no pigment = white

**Phenotype:** white

enzyme A \[\text{gene } a\]

enzyme B \[\text{gene } b\]
Independent Assortment

AABB $\otimes$ aabb or AAbb $\otimes$ aaBB
produces AaBb

Independent assortment in the $F_2$
produces ($-$ = indeterminate):

- $A-$ B- $\frac{3}{4} \times \frac{3}{4} = \frac{9}{16}$
- $A-$ bb $\frac{3}{4} \times \frac{1}{4} = \frac{3}{16}$
- aa B- $\frac{1}{4} \times \frac{3}{4} = \frac{3}{16}$
- aa bb $\frac{1}{4} \times \frac{1}{4} = \frac{1}{16}$
Dihybrid Ratios are Modified by Complementation

\[ AABB \odot aabb \text{ or } AAbb \odot aaBB \]
produces \( AaBb \) \( F_1 \)

\( F_2 \) produces:

\[ \begin{align*}
A^- B^- & = 9/16 \quad \rightarrow \quad 9/16 \text{ wildtype} \\
A^- bb & = 3/16 \\
aa B^- & = 3/16 \quad \bigg\} \quad 7/16 \text{ mutant} \\
aa bb & = 1/16
\end{align*} \]

Complementation: an interaction between two genes that are both necessary for expression of a phenotype
Dihybrid F₂

\[
\begin{align*}
\frac{9}{16} &= +/- +/- \quad \text{blue} \\
\frac{3}{16} &= +/- ¥/ ¥ \quad \text{white} \\
\frac{3}{16} &= £/ £ +/- \\
\frac{1}{16} &= £/ £ ¥ ¥'
\end{align*}
\]
Interaction between a regulatory protein and its target can also produce complementation:

<table>
<thead>
<tr>
<th>Normal</th>
<th>Regulatory gene</th>
<th>Gene for active protein</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$r^+$</td>
<td>$a^+$</td>
</tr>
</tbody>
</table>

both genes are necessary for expression of the phenotype
Interaction between a regulatory gene and its target

<table>
<thead>
<tr>
<th>Mutation in the gene that encodes the regulatory protein</th>
<th>Regulatory gene</th>
<th>Gene for active protein</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$r$</td>
<td>$a^+$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nonfunctional regulatory protein</td>
</tr>
<tr>
<td>Mutation in the gene that encodes the structural protein</td>
<td>$r^+$</td>
<td>$a$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mutation in both genes</td>
<td>$r$</td>
<td>$a$</td>
</tr>
</tbody>
</table>

- $r$: Regulatory gene
- $a$: Gene for active protein
- $r^+$: Mutated regulatory gene
- $a^+$: Mutated gene for active protein
Intermediate elements of a biochemical pathway may have a distinct phenotype
Biochemical Pathway: Petal Pigmentation

**Precursor:** no phenotype = white

enzyme 1 $\leftarrow$ allele $w^+$

**Intermediate:** pink pigment

enzyme 2 $\leftarrow$ allele $m^+$

**Product:** blue pigment
Biochemical Pathway: Petal Pigmentation

**Precursor**: no phenotype = white

**Intermediate**: pink pigment

**Phenotype**: pink

enzyme 1 \[ \rightarrow \] allele \( w^+ \)

enzyme 2 \[ \rightarrow \] allele \( m \) mutant = pink
Biochemical Pathway: Petal Pigmentation

**Precursor:** no phenotype = white

enzyme 1 ← allele *w*

mutant = white

**Intermediate:** pink pigment

enzyme 2 ← allele *m*^+^

**Phenotype:** white
Biochemical Pathway: Petal Pigmentation

Precursor: no phenotype = white

enzyme 1 allele $w$ mutant = white

Intermediate: pink pigment

enzyme 2 allele $m$ mutant = N/A

Phenotype: white
Dihybrid $w^+/w; m^+/m$  

Selfed

$\frac{9}{16} w^+/-; m^+/-$ Both enzymes active

$w^+$  

$\text{Enzyme 1}$  

$\text{Enzyme 2}$  

$9$

$\frac{3}{16} w^+/-; m/m$ Blocked at second enzyme

$w^+$  

$\text{Enzyme 1}$  

$3$

$\frac{3}{16} w/w; m^+/-$ Blocked at first enzyme

$m^+$  

$\text{Enzyme 2}$  

No substrate  

$4$

$\frac{1}{16} w/w; m/m$ Blocked at first enzyme
Modified Dihybrid Ratio with Recessive Epistasis

\[ \text{AABB } \otimes aabb \text{ or AAbb } \otimes aaBB \]

produces \( \text{AaBb } F_1 \)

\[ F_2 \text{ produces:} \]

\[ \begin{align*}
  A^- B^- &= 9/16 \quad \rightarrow \quad 9/16 \text{ wildtype - blue} \\
  A^- bb &= 3/16 \quad \rightarrow \quad 3/16 \text{ mutant}_2 - \text{ pink} \\
  aa B^- &= 3/16 \\
  aa bb &= 1/16
\end{align*} \]

\[ \{ 4/16 \text{ mutant}_1 - \text{ white (colorless)} \} \]
Coat color genes interact epistatically: 
*B and C genes in mammals*

$B/-; C/-$  
$b/b; C/-$  
$-/-; c/c$

Recessive epistasis: recessive phenotype for *C* gene masks genotypic variation for *B* gene –

– Expressed gene is epistatic to the masked gene

(C is epistatic to *B*)
Biochemical Pathway: Black Coat

Precursor: no pigment

Intermediate: brown pigment

Phenotype: black coat

enzyme “C” → gene C

enzyme “B” → gene B
blocked in brown coat

www.adapaproject.org/doggenetics/
Modified Dihybrid Ratio with Recessive Epistasis

\[ CCBB \, \otimes \, ccbb \, \text{or} \, CCbb \, \otimes \, ccBB \]

black \quad \text{albino} \quad \text{brown} \quad \text{albino}

produces \( CcBb \) (black) \( F_1 \)

\( F_2 \) produces:

\[ C- \, B- \, = \, 9/16 \quad \longrightarrow \quad 9/16 \, \text{black} \]
\[ C- \, bb \, = \, 3/16 \quad \longrightarrow \quad 3/16 \, \text{brown} \]
\[ cc \, B- \, = \, 3/16 \]
\[ cc \, bb \, = \, 1/16 \quad \bigg\} \quad 4/16 \, \text{albino} \]
Coat color genes interact epistatically: $B$ and $E$ genes in mammals

$B/-; E/-$  $b/b; E/-$  $-/-; e/e$
Several crosses in which yellow dogs were mated to brown ones produced all black in the F₁.

- What were the genotypes of the parents and the F₁?
- What would be the phenotypic ratio in the F₂?
Foxgloves illustrate different kinds of gene interactions and modification of Mendelian ratios
Dominant Epistasis

A dominant allele of one gene masks allelic variation in another gene

\[-/-; W/- \quad d/d; w/w \quad D/-; w/w\]

\(M\) - anthocyanin synthesis

\(D\) - modifier of \(M\)

\(W\) - prevents deposition of pigment
Modified Dihybrid Ratio with Dominant Epistasis

\[ WWDD \times wwdd \text{ or } WWdd \times wwDD \]
produces \( WwDd \) \( F_1 \)

Intercross \( F_1 \) produces \( F_2 \):

\[
\begin{align*}
W- D- &= 9/16 \quad \text{(12/16 white)} \\
W- dd &= 3/16 \\
ww D- &= 3/16 \quad \text{3/16 purple} \\
ww dd &= 1/16 \quad \text{1/16 lavender}
\end{align*}
\]
Recessive Epistasis

*M* - anthocyanin synthesis

*D* - modifier of *M*

*W* - prevents deposition of pigment

\[
\begin{align*}
M/M; D/D & \quad \times \quad m/m; d/d \\
\text{purple} & \quad \rightarrow \quad \text{white} \\
F_1 & = \text{all purple} \\
F_2 & = \frac{9}{16} \text{ } M/-; D/- \rightarrow \text{ purple} \\
& \quad \frac{3}{16} \text{ } M/-; d/d \rightarrow \text{ lavender} \\
& \quad \frac{3}{16} \text{ } m/m; D/- \} \quad \text{white} \\
& \quad \frac{1}{16} \text{ } m/m; d/d \}
\end{align*}
\]
Suppression: one gene can *suppress* the expression of another gene

- **Dominant Suppression**
  - Dominant suppressor reverses the dominant (wildtype) expression of another gene to a mutant expression

- **Recessive Suppression**
  - Recessive suppressor reverses the recessive (mutant) expression of another gene to a wildtype expression

- Both are characterized by 13:3 ratios in the $F_2$
### Modified Dihybrid Ratios with Suppression

#### Dominant Suppression:
M = purple petal exterior, m = white  
W = prevents pigment deposition

<table>
<thead>
<tr>
<th>Partial F₂ Genotype</th>
<th>Flower Petal Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>9/16 W/-; M/-</td>
<td>white</td>
</tr>
<tr>
<td>3/16 W/-; m/m</td>
<td>white</td>
</tr>
<tr>
<td>3/16 w/w; M/-</td>
<td>purple</td>
</tr>
<tr>
<td>1/16 w/w; m/m</td>
<td>white</td>
</tr>
</tbody>
</table>

### Recessive Suppression:
pd⁺ = wildtype eyes, pd = purple eyes  
su = recessive suppressor of pd

<table>
<thead>
<tr>
<th>Partial F₂ Genotype</th>
<th>Eye Color Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>9/16 pd⁺/-; su⁺/-</td>
<td>wildtype</td>
</tr>
<tr>
<td>3/16 pd⁺/-; su/su</td>
<td>wildtype</td>
</tr>
<tr>
<td>3/16 pd/pd; su⁺/-</td>
<td>purple</td>
</tr>
<tr>
<td>1/16 pd/pd; su/su</td>
<td>wildtype</td>
</tr>
</tbody>
</table>
Modified Dihybrid Ratios with Suppression

Dominant Suppression:
M = purple petal exterior, m = white
W = prevents pigment deposition

<table>
<thead>
<tr>
<th>Partial F₂ Genotype</th>
<th>Flower Petal Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>9/16 W/-; M/-</td>
<td>white</td>
</tr>
<tr>
<td>3/16 W/-; m/m</td>
<td>white</td>
</tr>
<tr>
<td>3/16 w/w; M/-</td>
<td>purple</td>
</tr>
<tr>
<td>1/16 w/w; m/m</td>
<td>white</td>
</tr>
</tbody>
</table>

Recessive Suppression:
pd⁺ = wildtype eyes, pd = purple eyes
su = recessive suppressor of pd

<table>
<thead>
<tr>
<th>Partial F₂ Genotype</th>
<th>Eye Color Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>9/16 pd⁺/-; su⁺/-</td>
<td>wildtype</td>
</tr>
<tr>
<td>3/16 pd⁺/-; su/su</td>
<td>wildtype</td>
</tr>
<tr>
<td>3/16 pd/pd; su⁺/-</td>
<td>purple</td>
</tr>
<tr>
<td>1/16 pd/pd; su/su</td>
<td>wildtype</td>
</tr>
</tbody>
</table>
## Modified Dihybrid Ratios with Suppression

### Dominant Suppression:
- **M** = purple petal exterior, **m** = white
- **W** = prevents pigment deposition

<table>
<thead>
<tr>
<th>Partial F₂ Genotype</th>
<th>Flower Petal Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>9/16 <strong>W/-; M/-</strong></td>
<td>white</td>
</tr>
<tr>
<td>3/16 <strong>W/-; m/m</strong></td>
<td>white</td>
</tr>
<tr>
<td>3/16 <strong>w/w; M/-</strong></td>
<td>purple</td>
</tr>
<tr>
<td>1/16 <strong>w/w; m/m</strong></td>
<td>white</td>
</tr>
</tbody>
</table>

### Recessive Suppression:
- **pd⁺** = wildtype eyes, **pd** = purple eyes
- **su** = recessive suppressor of **pd**

<table>
<thead>
<tr>
<th>Partial F₂ Genotype</th>
<th>Eye Color Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>9/16 <strong>pd⁺/-; su⁺/-</strong></td>
<td>wildtype</td>
</tr>
<tr>
<td>3/16 <strong>pd⁺/-; su/su</strong></td>
<td>wildtype</td>
</tr>
<tr>
<td>3/16 <strong>pd/pd; su⁺/-</strong></td>
<td>purple</td>
</tr>
<tr>
<td>1/16 <strong>pd/pd; su/su</strong></td>
<td>wildtype</td>
</tr>
</tbody>
</table>

**Phenotype modified by suppression**
# Modified Dihybrid Ratios with Suppression

<table>
<thead>
<tr>
<th>Partial Genotype</th>
<th>Dominant Suppression (3 wt: 13 mut)</th>
<th>Recessive Suppression (13 wt: 3 mut)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 $A^{-} ; Su^{-}$</td>
<td>Mutant</td>
<td>Wildtype</td>
</tr>
<tr>
<td>3 $A^{-} ; su; su$</td>
<td>Wildtype</td>
<td>Wildtype</td>
</tr>
<tr>
<td>3 $a; a ; Su^{-}$</td>
<td>Mutant</td>
<td>Mutant</td>
</tr>
<tr>
<td>1 $a; a ; su; su$</td>
<td>Mutant</td>
<td>Wildtype</td>
</tr>
</tbody>
</table>

Phenotype modified by suppression
### Modified Dihybrid Ratios with Suppression

<table>
<thead>
<tr>
<th>Partial Genotype</th>
<th>Dominant Suppression (3 wt: 13 mut)</th>
<th>Recessive Suppression (13 wt: 3 mut)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 A - ; Su -</td>
<td>Mutant</td>
<td>Wildtype</td>
</tr>
<tr>
<td>3 A - ; su su</td>
<td>Wildtype</td>
<td>Wildtype</td>
</tr>
<tr>
<td>3 a a ; Su -</td>
<td>Mutant</td>
<td>Mutant</td>
</tr>
<tr>
<td>1 a a ; su su</td>
<td>Mutant</td>
<td>Wildtype</td>
</tr>
</tbody>
</table>

**Phenotype modified by suppression**
A cross with dominant suppression

true white $\times$ true white

$A/A; B/B \rightarrow a/a; b/b$

$F_1 = \text{all white } A/a; B/b$

$F_2 = \begin{array}{c}
9/16 A/-; B/- \\
3/16 A/-; b/b \\
3/16 a/a; B/- \\
1/16 a/a; b/b
\end{array} \{ \begin{array}{c}
\rightarrow \text{white} \\
\rightarrow \text{purple} \\
\rightarrow \text{white}
\end{array}$
Analysis of Gene Interactions:

If the biochemical mechanism for the interaction is known, the ratio of partial genotypes and phenotypes can be determined.

If the phenotypic ratio is known, the mechanism for the interaction can be determined.
Interactions of genes in pathways:

Complementation
9:7 $F_2$

Recessive Epistasis
9:3:4 $F_2$
disk $\otimes$ long,
$F_1 = \text{all disk}$
$F_2 =$

32 long  178 sphere  270 disk

Long  Sphere  Disk
Red is normal petal pigmentation, orange and white are variants found in nature

<table>
<thead>
<tr>
<th>Parents</th>
<th>$F_1$</th>
<th>$F_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>red x white</td>
<td>red</td>
<td>101 red, 33 white</td>
</tr>
<tr>
<td>red x orange</td>
<td>red</td>
<td>192 red, 63 orange</td>
</tr>
<tr>
<td>orange x white</td>
<td>red</td>
<td>272 red, 121 white, 89 orange</td>
</tr>
</tbody>
</table>
Interactions between Phenotypes of Genes in Different Pathways

Products from two pathways are added together or superimposed.

This interaction produces a 9:3:3:1 $F_2$ ratio that includes novel phenotypes not present in parents or $F_1$. 
black $\otimes$ orange

$\downarrow$

$F_1 = $ camouflage

$\downarrow$

$F_2 =$

9 camouflage
3 orange
3 black
1 pink (albino)
brown \( \otimes \) vermilion

\[ \downarrow \]

\[ F_1 = \text{red (wildtype)} \]

\[ \downarrow \]

\[ F_2 = \]

\[ 9/16 \quad \text{wildtype} \]

\[ 3/16 \quad \text{brown} \]

\[ 3/16 \quad \text{vermilion} \]

\[ 1/16 \quad \text{white} \]
Interacting mutations affect eye color in *Drosophila*

- **(a) All genes normal**
  - Pool of precursor molecules
  - Normal *vermilion* gene → normal pigment
  - Normal *brown* gene → bright red pigment
  - Normal *white* gene → red eyes

- **(b) One mutant gene: *vermilion***
  - Pool of precursor molecules
  - Mutant *vermilion* gene → no brown pigment
  - Normal *brown* gene → bright red pigment
  - Normal *white* gene → vermillion eyes

- **(c) One mutant gene: *brown***
  - Pool of precursor molecules
  - Normal *vermilion* gene → brown pigment
  - Mutant *brown* gene → no bright red pigment
  - Normal *white* gene → brown eyes
• Multiple genes affect eye color
• Some of the genes interact
• White eyes can be caused by more than one genotype (\(w\) or \(cn\ \text{bw}\))
black $\otimes$ cinnamon

$F_1 = \text{all agouti}$

$F_2 = 9 \text{ agouti}$

3 black
3 cinnamon
1 brown

$B/-; a/a = \text{black}$

$B/-; A/- = \text{agouti}$

$b/b; A/- = \text{cinnamon}$

$b/b; a/a = \text{brown}$
Modifier Genes (D gene)

Genotype | Phenotype
---|---
Chestnut + D/D | Chestnut
Chestnut + D/d | Palomino
Chestnut + d/d | Cremello (nearly white)
Bay + D/D | Bay
Bay + D/d | Dun or buckskin
Bay+ d/d | Perlino (nearly white)
Mammalian Coat Color Genes

A gene: yellow band present or absent
B gene: black vs. brown pigment
C gene: presence or absence of pigment
D gene: modifier, incomplete dominance
E gene: deposition of pigment in fur
S gene: $S^P = $ white patches
Human Eye Color Variation

blue – brown polymorphism: 
*HERC2* regulatory gene effects
expression of the *OCA2* gene in iris
  – brown = full *OCA2* expression
  – blue = very low *OCA2* expression

blue/gray variation due to different
light scattering by the iris
  – there are no blue, gray (or green)
pigments

albino: mutant *OCA2* gene (no
pigment expression, not limited
to eyes)
Interaction between *HERC2* and *OCA2*

*HERC2* regulatory gene effects expression of the *OCA2* gene in iris

- brown = full *OCA2* expression
- blue = very low *OCA2* expression

Both genes are necessary for expression of the melanin pigments in iris
Human Eye Color Variation

brown polymorphisms (dark brown to green) controlled by interactions among 16 genes controlling pigment deposition, including HERC2 and different alleles of OCA2

- green = light brown + scattering (like blue)
- hazel = light brown + different pigmentation patterns within the iris

a ring of pigment in the iris can cause apparent eye color changes as the pupil dilates or in different light