Basic Genetics (SQBS 2753)

Extensions of Mendelism

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Beyond Mendel…

- Since Mendel's work was rediscovered in the early 1900's:
  - Researchers have studied the many ways genes influence an individual's phenotype
  - These investigations are called neo-Mendelian genetics (neo from Greek for "new")
  - This chapter examines types of inheritance observed by researchers that did not conform to the expected Mendelian ratios

Extensions of Mendelian Genetics

- How alleles affect phenotype
  - Not always simple dominant/recessive issue
- Gene interaction
  - Phenotype controlled by more than one gene
- Sex-linked genes (X-linkage in X/Y organisms)
- Phenotype can depend on more than genotype
  - Environmental effects

Extended Mendelian Inheritance Patterns

- Incomplete dominance
  - Heterozygosity at a locus produces a third 3 phenotype intermediate to the two homozygous phenotypes
- Co-dominance
  - Heterozygosity at a locus produces a single unique phenotype different from either homozygous condition
- Overdominance
  - Heterozygosity at a locus creates a phenotype that is more beneficial or more deterimental than homozygosity of either locus with any allele

Extended Mendelian Inheritance Patterns

- Lethality
  - Homozygosity of an allele kills the cell or organism
- Penetrance
  - A measure of how variation in expression of a given allele occurs
  - incomplete penetrance describes the lack of effect a deleterious allele might have in an individual carrying it

Extended Mendelian Inheritance Patterns

- Sex-linked
  - inheritance of genes on that are unique to a sex chromosomes
  - pseudoautosomal genes – genes on both sex chromosomes appear to be on autosomes
- Sex-influenced
  - An allele is expressed differently in each sex. Behaving dominantly in one sex and recessively in the other
- Sex-limited
  - An allele is only expressed in one or the other sex

EXTENSIONS TO MENDEL FOR SINGLE-GENE INHERITANCE

Complete Dominance/Recessiveness

- recessive allele does not affect the phenotype of the heterozygote
- two possible explanations
  - 50% of the normal protein is enough to accomplish the protein's cellular function
  - The normal gene is "up-regulated" to compensate for the lack of function of the defective allele

Simple Mendelian Inheritance

Normal/dominant alelle: P (purple)
Recessive/defective alelle: p (white)

Genotype	PP	Pp	pp
Amount of functional protein	100%	50%	0%
Phenotype	Purple	Purple	White

Incomplete Dominance

- Heterozygote exhibits a phenotype intermediate to the homozygote
- Also called *intermediate dominance* or dosage effect
- Example: Flower colour of snapdragon
- Phenotypic ratio: 1 (red) :2 (pink):1 (white) and NOT the 3:1 ratio

Phenotype	Genotype	Amount of gene product
Red	RR	2X
Pink	Rr	X
White	rr	0

Gene Dosage – A form of intermediate dominance

- Alleles of white –
  - X-linked eye color gene in *Drosophila*
  - W – red (wildtype gene)
  - w - white
  - we - eosin
- we allele was expressed with different intensity in the two sexes
  - Homozygous females → eosin
  - Males → light-eosin

Gene Dosage

- Morgan & Bridges hypothesized that difference in intensity was due to the difference in number of X chromosomes
  - Female has two copies of the “eosin color producer” allele
    - Eyes will contain more color
  - Males have only one copy of the allele
    - Eyes will be paler
- This is an example of gene dosage effect

Codominance

- – two alleles at a locus produce different and detectable gene products in heterozygote
- – No dominance or recessiveness
- – No "blended" phenotype (not incomplete dominance)
- Example: MN blood group in humans
  - – Red blood cell glycoprotein surface antigen has two forms (M and N)
  - – An individual may exhibit either or both

Codominance

For example:

- One serum (anti-M) recognises only the M antigen; anti-N recognises only N antigen
- Antigen M reacts with anti-M causes AGGLUTINATION

Genotype	Phenotype
$L^{M}L^{M}$	MM
$L^{M}L^{N}$	MN
$L^{N}L^{N}$	NN

Multiple Alleles

- The term multiple alleles is used to describe situations when three or more different alleles of a gene exist
- Examples:
  - – ABO blood
  - – Coat color in many species
  - – Eye color in *Drosophila*

Multiple Alleles

- **ABO blood** phenotype is determined by multiple alleles
- ABO type result of antigen on surface of RBCs
  - Antigen A, which is controlled by allele I^A
  - Antigen B, which is controlled by allele I^B
  - Antigen O, which is controlled by allele i

Blood Type	**O**	**A**	**B**	**AB**
Genotype	ii	I^AI^A or I^Ai	I^BI^B or I^Bi	I^AI^B
Surface Antigen	O	A	B	A and B

Allelic Series

- Dominance hierarchy will exist for multiple alleles
  - allelic series for ABO type
    - $I^A = I^B > i$
  - allelic series for rabbit coat color alleles :
    - $C > c^{ch} > c^h > c$

Allelic Series

- **coat color** in rabbits
  - C (full coat color)
  - c^{ch} (chinchilla pattern of coat color)
    - Partial defect in pigmentation
  - c^{h} (himalayan pattern of coat color)
    - Pigmentation in only certain parts of the body
  - c (albino)
    - Lack of pigmentation

Allelic Series

- Four alleles, c gene in rabbits ---> six heterozygotes;
- C^{+} : completely dominant
- C^{ch} (chinchila allele): partly dominant over the himalayan and albino alleles
- Dominance relationship:

$$C^{+} > C^{ch} > C^{h} > C$$

- *C* gene – formation of black pigment in fur;
- *Albino* allele – nonfunctional allele = null =amorphic (completely recessive)
- Partly functional allele = hypomorphic

Coat Colour in Rabbit

Rabbit	Genotype	Phenotype
Albino	CC	White hairs over the entire body
Himalayan	C^hC^h	Black hairs on the extremities; white hairs everywhere else
Chinchilla	$C^{ch}C^{ch}$	White hair with black tips on the body
Wild-type	C^+C^+	Coloured hairs over the entire body

Lethal Alleles

- Essential genes are those that are absolutely required for survival
  - The absence of their protein product leads to a lethal phenotype
    - It is estimated that about 1/3 of all genes are essential for survival
- Nonessential genes are those not absolutely required for survival
- A lethal allele is one that has the potential to cause the death of an organism
  - These alleles are typically the result of mutations in essential genes
  - usually recessive, but can be dominant

Lethal Alleles

- Example: agouti (coat color) in mice
  - agouti x agouti → all agouti
  - yellow x yellow → 2/3 yellow, 1/3 agouti
  - agouti x yellow → ½ yellow, ½ agouti
  - Explanation: mutant yellow dominant over wt agouti and homozygous agouti lethal. Mutant allele always on (gain of function), deletion actually affects neighboring essential gene

Yellow $A^y A^+$ × Yellow $A^y A^+$

⇩

Eggs \ Sperms	A^+	A^y
A^+	A^+A^+ *(Gray-Brown or agouti)*	A^+A^y *(Yellow)*
A^y	A^+A^y *(Yellow)*	A^yA^y *(Embryonic lethality)*

Lethal Dominant Mutations

- Both homozygous and heterozygous states are lethal
- Generally very rare
- Example: Huntington disease (humans)
  - Nervous and motor system degeneration
  - Commonly begins to be exhibited after age forty (but can be much earlier)
    - Children already born
- Afflicted persons are heterozygous (Hh)

Conditional Mutations

- The ch allele is a temperature-sensitive conditional mutant
  - The enzyme is only functional at low temperatures
  - Therefore, dark fur will only occur in cooler areas of the body

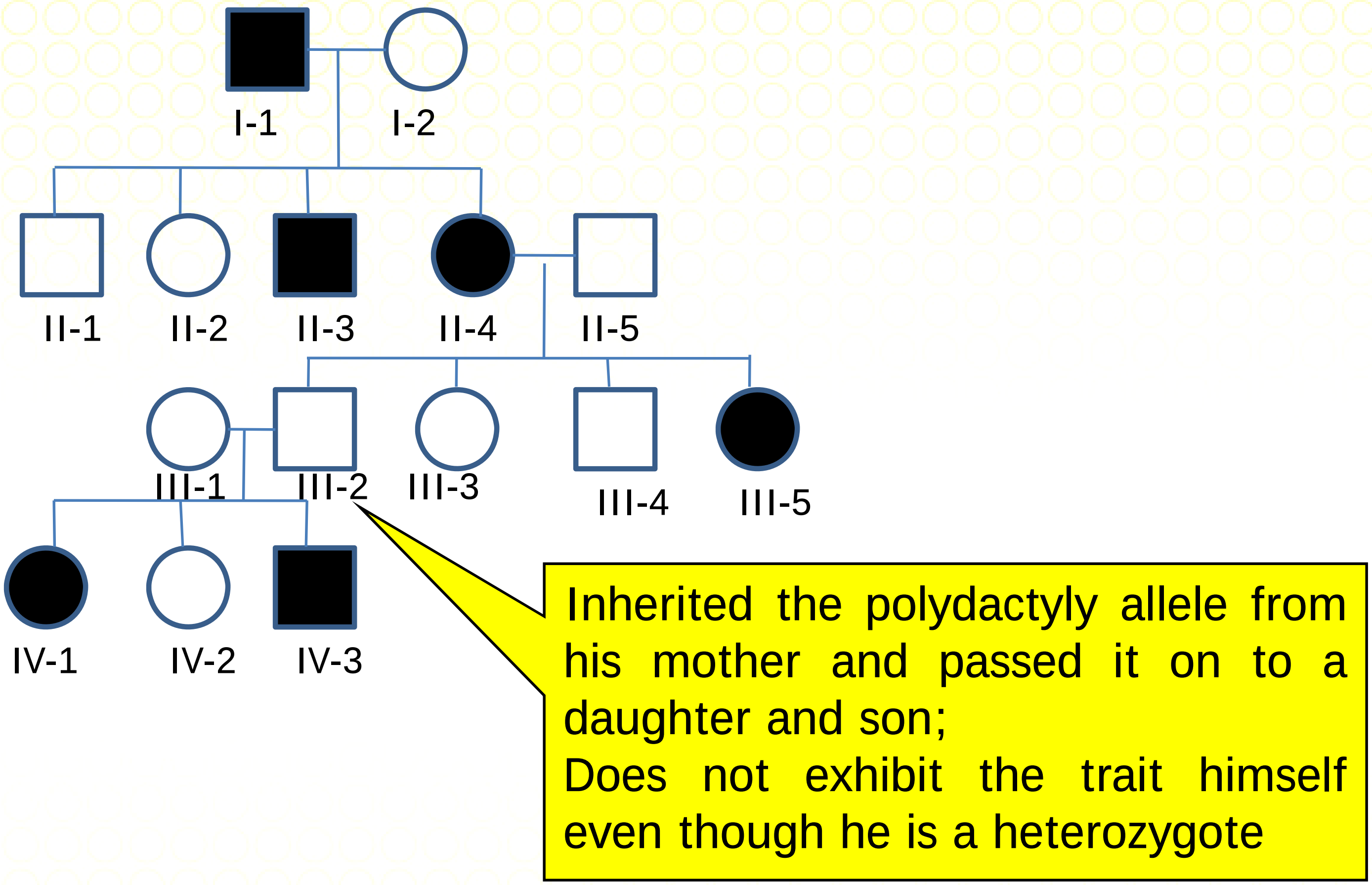
Overdominance

- Overdominance is the phenomenon in which a heterozygote is more vigorous than both of the corresponding homozygotes

- Example:
  - Sickle-cell heterozygotes are resistant to malaria
  - increased disease resistance in plant hybrids

Incomplete Penetrance

- In some instances, a dominant allele is not expressed in a heterozygote individual
- Example = Polydactyly
  - Autosomal dominant trait
  - Affected individuals have additional fingers and/or toes
  - A single copy of the polydactyly allele is usually sufficient to cause this condition
  - In some cases, however, individuals carry the dominant allele but do not exhibit the trait


I-1
I-2
II-1
II-2
II-3
II-4
II-5
III-1
III-2
III-3
III-4
III-5
IV-1
IV-2
IV-3
Inherited the polydactyly allele from his mother and passed it on to a daughter and son;
Does not exhibit the trait himself even though he is a heterozygote

Incomplete Penetrance

- The term indicates that a dominant allele does not always "penetrate" into the phenotype of the individual
- The measure of penetrance is described at the population level
  - If 60% of heterozygotes carrying a dominant allele exhibit the trait allele, the trait is 60% penetrant
- Note:
  - In any particular individual, the trait is either penetrant or not

Expressivity

- Expressivity is the degree to which a trait is expressed
- In the case of polydactyly, the number of extra digits can vary
  - A person with several extra digits has high expressivity of this trait
  - A person with a single extra digit has low expressivity

Expressivity

- “Eyeless” mutation in *Drosophila*
  - Reduces eye size from a partial reduction to complete elimination (average 0.25 to 0.50)

Penetrance & Expressivity

- The molecular explanation of expressivity and incomplete penetrance may not always be understood
- In most cases, the range of phenotypes is thought to be due to influences of the
  - Environment

    and/or
  - Other genes (genetic background)

Environmental Effects

- Temperature effects
  - Evening primrose produces red flowers at 23°C and white flowers at 18°C
  - Siamese cats and Himalayan rabbits have darker fur on cooler areas of body (tail, feet, ears)
    - Enzymes lose catalytic function at higher temperature
- Temperature sensitive mutations
  - Mutant allele only expressed (phenotype) at [generally] lower temperature
  - ts phage mutants, restrictive and permissive temperatures
- Heat-shock genes

Nutritional Effects

- Nutritional mutations
  - Prevent synthesis of nutrient molecules
  - Auxotrophs
  - Phenotype expressed or not depending upon the diet
- Phenylketonuria (PKU) – recessive disorder of amino acid metabolism
  - Loss of enzyme to metabolize phenylalanine
  - Severe problems unless low Phe diet
- Galactosemia (very bad again) and lactose intolerance (unpleasant)…

Environmental Effects on the Expression of Human Genes

- Pattern baldness – sex-influenced
- Both homo- and heterozygotes – bald patches (male);
- Female – homozygotes – bald (thinning of the hair)
- Relate to testosterone

GENE INTERACTIONS

Epistatic Gene Interactions

- Gene interactions occur when two or more different genes influence the outcome of a single trait
- Most morphological traits (height, weight, color) are affected by multiple genes
- Epistasis describes situation between various alleles of two genes
- Quantitative loci is a term to describe those loci controlling quantitatively measurable traits
- Pleiotropy describes situations where one gene affects multiple traits

Epistasis

- Epistasis
  - The effect of one gene pair (locus) masks or modifies the effect of another gene pair
- Examples
  - Recessive alleles at one locus override expression of alleles at another locus. Alleles at 1st locus are said to be epistatic to the masked hypostatic alleles at the 2nd locus
  - Allele(s) at one locus may require specific allele at another locus, these pairs are said to complement each other

Epistatic Gene Interactions

- examine cases involving 2 loci (genes) that each have 2 alleles
- Crosses performed can be illustrated in general by
  - AaBb X AaBb
  - Where A is dominant to a and B is dominant to b
- If these two genes govern two different traits
  - A 9:3:3:1 ratio is predicted among the offspring
  - simple Mendelian dihybrid inheritance pattern
- If these two genes do affect the same trait the 9:3:3:1 ratio may be altered
  - **9:3:4,** or **9:7,** or **9:6:1,** or **8:6:2** or **12:3:1,** or **13:3,** or **15:1**
  - epistatic ratios

A Cross Producing a 9:7 ratio

White Variety, ***CCpp*** × White Variety, ***ccPP***

⇩

F$_1$ — All purple, ***CcPp***

⇩

SELF-FERTILIZATION

⇩

F$_2$ progeny

	CP	*Cp*	*cP*	*cp*
CP	*CCPP* Purple	*CCPp* Purple	*CcPP* Purple	*CcPp* Purple
Cp	*CCPp* Purple	*CCpp* White	*CcPp* Purple	*Ccpp* White
cP	*CcPP* Purple	*CcPp* Purple	*ccPP* White	*ccPp* White
cp	*CcPp* Purple	*Ccpp* White	*ccPp* White	*ccpp* White

9 C_P_ : 3 C_pp :3 ccP_ : 1 ccpp

purple (9 C_P_) ; white (3 C_pp : 3 ccP_ : 1 ccpp)

Duplicate Recessive Genes (9:7)

- When identical phenotypes are produced by both homozygous recessive genotypes, the F1 ratio becomes 9:7.
- The genotype *aaB-, A-bb & aabb* produce one phenotype.
- Both dominant alleles, when present together, complement each other & produce a different phenotype.

- For example:

Flower color of sweet peas

A- codes for color pigment
B codes for color purple
b codes for color white

Duplicate Recessive Genes (9:7)

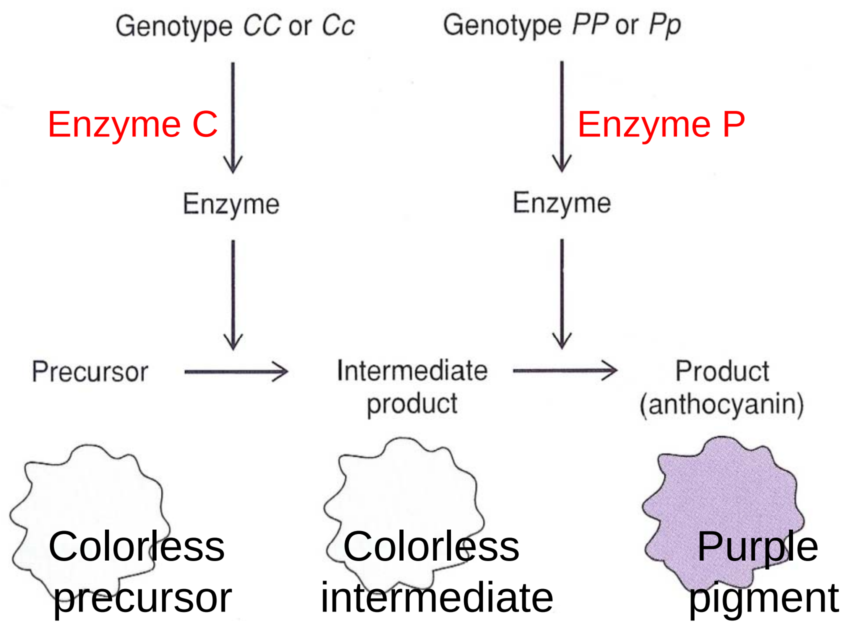
- P: *AAbb (white) X aaBB (white)*

  F_1: *AaBb (purple)*

F_2	**AB**	**Ab**	**aB**	**ab**
AB	*AABB, purple*	*AABb, purple*	*AaBB, purple*	*AaBb, purple*
Ab	*AABb, purple*	*AAbb, white*	*AaBb, purple*	*Aabb, white*
aB	*AaBB, purple*	*AaBb, purple*	*aaBB, white*	*aaBb, white*
ab	*AaBb, purple*	*Aabb, white*	*aaBb, white*	*aabb, white*

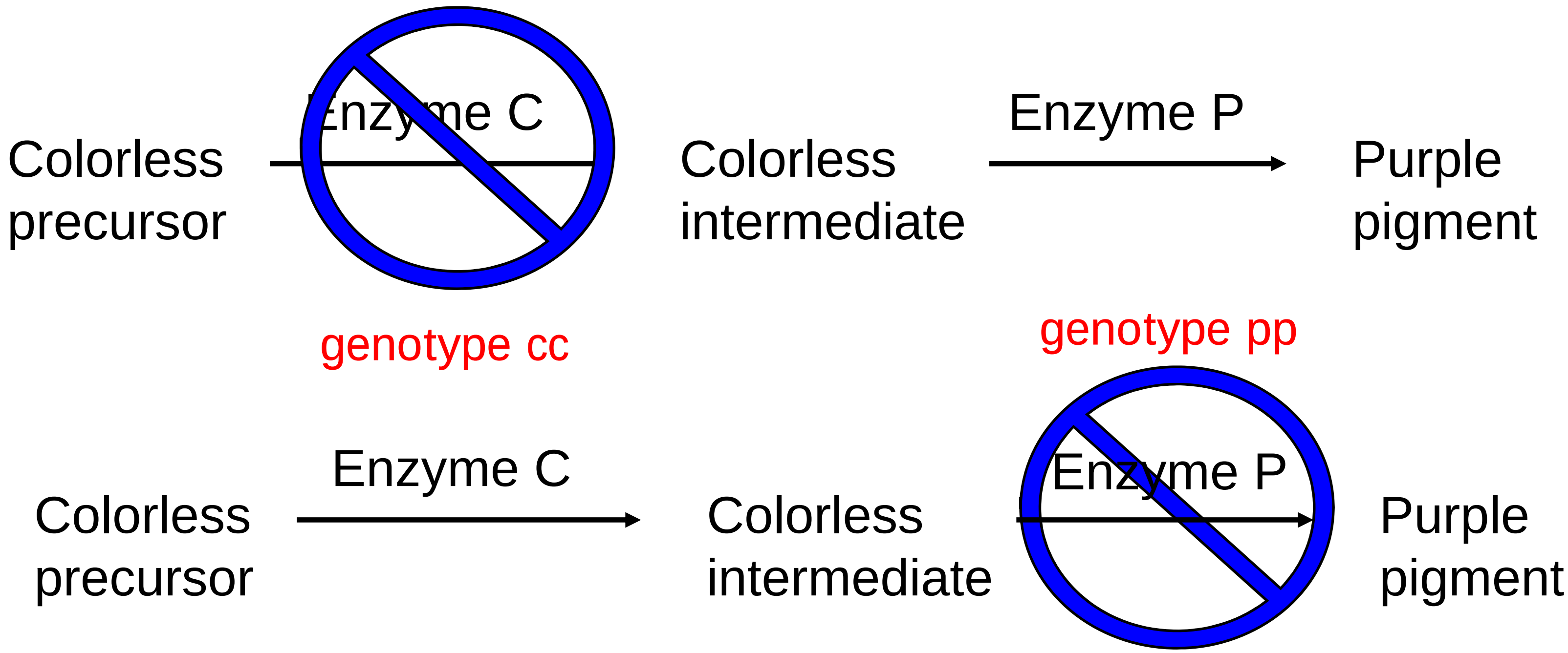
Epistatic Gene Interaction

- Complementary gene action
  - Enzyme C and enzyme P cooperate to make a product, therefore they complement one another



Epistatic Gene Interaction

- Epistasis describes the situation in which a gene masks the phenotypic effects of another gene
- Epistatic interactions arise because the two genes encode proteins that participate in sequence in a biochemical pathway
- If either loci is homozygous for a null mutation, none of that enzyme will be made and the pathway is blocked



A Cross Involving a Two-Gene Interaction Can Still Produce a 9:3:3:1 ratio

- Inheritance of comb morphology in chicken
  - First example of gene interaction
  - William Bateson and Reginald Punnett in 1906
  - Four different comb morphologies:
  - Rose, Pea, Walnut & Single

The crosses of Bateson and Punnett

Rose comb Wyandotte ***RRpp*** × Pea comb Brahma ***rrPP***

F_1 — All Walnut, ***RrPp***

SELF-FERTILIZATION

F_2 **progeny**

	RP	*Rp*	*rP*	*rp*
RP	*RRPP* *walnut*	*RRPp* *Walnut*	*RrPP* *Walnut*	*RrPp* *Walnut*
Rp	*RRPp* *Walnut*	*RRpp* *Rose*	*RrPp* *Walnut*	*Rrpp* *Rose*
rP	*RrPP* *Walnut*	*RrPp* *Walnut*	*rrPP* *Pea*	*rrPp* *Pea*
rp	*RrPp* *Walnut*	*Rrpp* *Rose*	*rrPp* *Pea*	*rrpp* *Single*

The crosses of Bateson and Punnett

- F_2 generation consisted of chickens with four types of combs
  - 9 walnut : 3 rose : 3 pea : 1 single
- Bateson and Punnett reasoned that comb morphology is determined by two different genes
  - R (rose comb) is dominant to r
  - P (pea comb) is dominant to p
  - R and P are codominant (walnut comb)
  - rrpp produces single comb

Duplicate Dominant Gene (15:1)

- The 9:3:3:1 ratio is modified if the dominant alleles of both loci each produce the same phenotype without cumulative effect.

- For example:

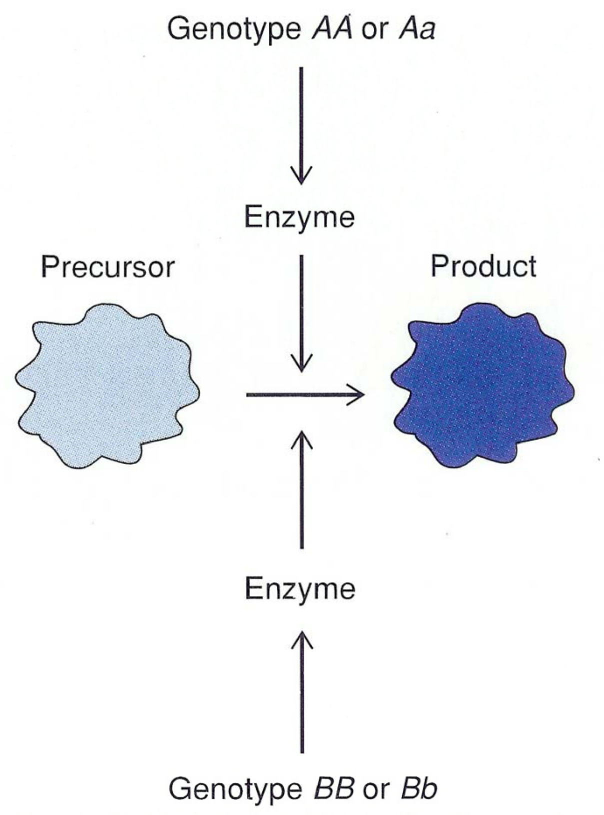
Flower color of peas
aabb codes for color white
any other combination produce color red

P: *AAbb (red)* *X* *aaBB (white)*
F_1: *AaBb* (red)

F_2		***AB***	***Ab***	***aB***	***ab***
	AB	*AABB, red*	*AABb, red*	*AaBB, red*	*AaBb, red*
	Ab	*AABb, red*	*AAbb, red*	*AaBb, red*	*Aabb, red*
	aB	*AaBB, red*	*AaBb, red*	*aaBB, red*	*aaBb, red*
	ab	*AaBb, red*	*Aabb, red*	*aaBb, red*	*aabb, white*

Gene Interaction

- Duplicate gene action
  - Enzyme 1 and enzyme 2 are redundant
  - They both make product C, therefore they duplicate each other



Dominant Epistasis (12:3:1)

- When the dominant allele (*A*) produces a certain phenotype regardless of the allele condition of another locus (*B*), ***A* is said to be epistatic to *B***.
- The dominant allele *A* is able to express itself in the presence of either *B* or *b*.
- Only when the genotype of the individual is **homozygous recessive (*aa*), then *B* or *b* can be expressed.**
- *A-B- & A-bb* produce the same phenotype;
- *aaB- & aabb* produce 2 additional phenotypes.

Dominant Epistasis (12:3:1)

- For example:

Coat colors of dogs

I- inhibit coat color pigment / expression

B represents **black** color coat

b represents **brown** color coat

P: ***IiBb*** *(white)* *X* ***IiBb*** *(white)*

F_1: *IiBb*

F_2		IB	Ib	iB	ib
	IB	*IIBB, white*	*IIBb, white*	*IiBB, white*	*IiBb, white*
	Ib	*IIBb, white*	*IIbb, white*	*IiBb, white*	*Iibb, white*
	iB	*IiBB, white*	*IiBb, white*	*iiBB, black*	*iiBb, black*
	ib	*IiBb, white*	*Iibb, white*	*iiBb, black*	*iibb, brown*

Recessive Epistasis (9:3:4)

- If the recessive genotype at locus A (eg: ***aa***) suppresses the expression of alleles at B locus, **locus A exhibit recessive epistasis over locus B**.

- The alleles in **locus B can only be expressed** with the presence of dominant alleles at locus A.

- Genotypes ***A-B- & A-bb*** produce 2 additional phenotypes.

- For example:

  Flower color of peas

  A- codes for color pigment

  B codes for color **purple**

  b codes for color **red**

•

Recessive Epistasis (9:3:4)

P: ***AAbb* (*red*)** *X* ***aaBB* (*white*)**

F_1: *AaBb* (***purple***)

F_2	**AB**	**Ab**	**aB**	**ab**
AB	*AABB, purple*	*AABb, purple*	*AaBB, purple*	*AaBb, purple*
Ab	*AABb, purple*	*AAbb, red*	*AaBb, purple*	*Aabb, red*
aB	*AaBB, purple*	*AaBb, purple*	*aaBB, white*	*aaBb, white*
ab	*AaBb, purple*	*Aabb, red*	*aaBb, white*	*aabb, white*

Duplicate Genes with Cumulative Effect (9:6:1)

- Occur when dominant allele (homozygous or heterozygous) at either locus (but not both) produces the same phenotype.
- Genotypes *A-bb & aaB-* produce one unit each and therefore have the same phenotype.
- Genotype *aabb* produces no pigment but in genotype *A-B-* the effect is cumulative and 2 units of phenotypes are produced.

- For example:

  Color of wheat kernels

  R-B- produce red color

  rrbb produce white color

  Any other combination produces brown color

-

P: *RRBB (red)* X *rrbb (white)*

F_1: *RrBb (red)*

F_2

	RB	**Rb**	**rB**	**rb**
RB	*RRBB, red*	*RRBb, red*	*RrBB, red*	*RrBb, red*
Rb	*RRBb, red*	*RRbb, brown*	*RrBb, red*	*Rrbb, brown*
rB	*RrBB, red*	*RrBb, red*	*rrBB, brown*	*rrBb, brown*
rb	*RrBb, red*	*Rrbb, brown*	*rrBb, brown*	*rrbb, white*

Dominant and Recessive Interaction (13:3)

- Only two F2 phenotypes result when a dominant genotype at 1 locus (*A*-) and the recessive genotype at another (*bb*) produce the same phenotypic effect.
- Genotype *A-B-*, *aaB-* & *aabb* produce one phenotype and genotype *A-bb* produce another in the ratio 13:3.

F_2	**AB**	**Ab**	**aB**	**ab**
AB	*AABB, white*	*AABb, white*	*AaBB, white*	*AaBb, white*
Ab	*AABb, white*	*AAbb, red*	*AaBb, white*	*Aabb, red*
aB	*AaBB, white*	*AaBb, white*	*aaBB, white*	*aaBb, white*
ab	*AaBb, white*	*Aabb, red*	*aaBb, white*	*aabb, white*

Dominant and Recessive Interaction (13:3)

- Only two F2 phenotypes result when a dominant genotype at 1 locus (*A*-) and the recessive genotype at another (*bb*) produce the same phenotypic effect.
- Genotype *A-B-, aaB- & aabb* produce one phenotype and genotype *A-bb* produce another in the ratio 13:3.

Dominant and Recessive Interaction (13:3)

- For example:

<u>Flower color of peas</u>

A-bb codes for color red

Any other combination codes for color white

P: *AAbb (white)* *X* *aaBB (white)*

F_1: *AaBb (white)*

F_2	***AB***	***Ab***	***aB***	***ab***
AB	*AABB, white*	*AABb, white*	*AaBB, white*	*AaBb, white*
Ab	*AABb, white*	*AAbb, red*	*AaBb, white*	*Aabb, red*
aB	*AaBB, white*	*AaBb, white*	*aaBB, white*	*aaBb, white*
ab	*AaBb, white*	*Aabb, red*	*aaBb, white*	*aabb, white*

Summary of Epistatic Ratios

<table>
<tr><th>Genotypes</th><th>A-B-</th><th>A-bb</th><th>aaB-</th><th>aabb</th></tr>
<tr><td>Classical ratio</td><td>9</td><td>3</td><td>3</td><td>1</td></tr>
<tr><td>Dominant epistasis</td><td colspan="2">12</td><td>3</td><td>1</td></tr>
<tr><td>Recessive epistasis</td><td>9</td><td>3</td><td colspan="2">4</td></tr>
<tr><td>Duplicate genes with cumulative effect</td><td>9</td><td colspan="2">6</td><td>1</td></tr>
<tr><td>Duplicate dominant genes</td><td colspan="3">15</td><td>1</td></tr>
<tr><td>Duplicate recessive genes</td><td>9</td><td colspan="3">7</td></tr>
<tr><td>Dominant and recessive interaction</td><td>13</td><td>3</td><td colspan="2"></td></tr>
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Examples of Epistatic Cases

Organism	Character	F2 Phenotypes				Modified ratio
		9/16	3/16	3/16	1/16	
Mouse	Coat colour	Agouti	albino	Black	Albino	9:3:4
Squash	Colour	White		Yellow	Green	12:3:1
Pea	Flower colour	Purple	White			9:7
Squash	Fruit shape	Disc	Sphere		Long	9:6:1
Chicken	Colour	White		Coloured	White	13:3

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