Chapter 8 ~ Gene Interactions

Introductions

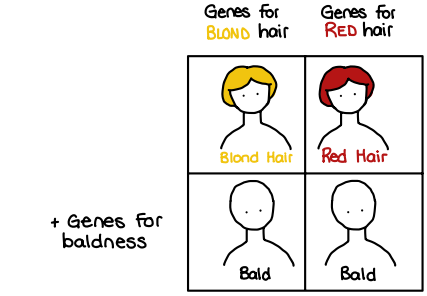
- Gene interaction occurs when genes at multiple loci determine a single phenotype:
  - when the effects of genes at one locus depend on the presence of genes at other loci.
  - The specific type of gene interaction whereby one gene masks the effect of another gene is called EPISTASIS
- There are two main types of epistasis:
  1. Dominant
  2. Recessive
- Generally, when epistasis is present, the four Mendelian genotypic classes (in a dihybrid cross) produce fewer than four observable phenotypes, because one gene masks the phenotypic effects of another.
  Often, the basis of epistasis is a gene pathway in which the expression of one gene depends on the function of a gene that precedes or follows it in the pathway.

Recessive Epistasis

- In recessive epistasis, the recessive allele of one gene masks the effects of either allele of the second gene

Dominant Epistasis

- In dominant epistasis, the dominant allele of one gene masks the effects of either allele of the second gene



- The principles of genetic analysis that we have described for a single locus (dominance/recessiveness) can be extended to the study of alleles at two different loci.
- While the analysis of two loci concurrently is required for genetic mapping, it can also reveal interactions b/w genes that affect the phenotype
- Understanding these interactions is useful for both basic & applied research
- Before discussing these interactions, we will first revisit Mendelian inheritance for two loci

Mendelian Dihybrid Crosses

Mendels Second Law:

- To analyze the segregation of two traits (ex: colour, wrinkle) at the same time, in the same individual, Mendel crossed a pure breeding line of green, wrinkled peas with a pure breeding line of yellow, round peas to produce F_1 progeny that were all green & round which were also dihybrids; they carried two alleles at each of two loci

- If the inheritance of seed color was truly independent of seed shape, then when the F_1 dihybrids were crossed to each other, a 3:1 ratio of one trait should be observed w/ each phenotypic class of the other trait
  - Using the product law, we would therefore predict that if:

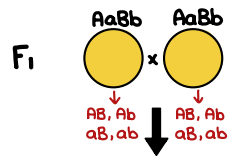
$3/4$ of the progeny = green
$3/4$ of the progeny = round
then
$\frac{3}{4} \times \frac{3}{4} = \frac{9}{16}$

$\frac{9}{16}$ the progeny would be both round & green

  - Likewise, $\frac{3}{4} \times \frac{1}{4} = \frac{3}{16}$ of the progeny would be both round & yellow, and so on.
  - By applying the product rule to all these combinations of phenotypes, we can predict a 9:3:3:1 phenotypic ratio among the progeny of a dihybrid cross, if certain conditions are met, including the independent segregation of the alleles at each locus.

9:3:3:1 is very close to the ratio Mendel observed in his studies of dihybrid crosses → states his Second Law, the LAW OF INDEPENDENT ASSORTMENT,

we now express as follows: two loci assort independently of each other during gamete formation



F_2	AB	Ab	aB	ab
AB	AABB	AABb	AaBB	AaBb
Ab	AABb	AAbb	AaBb	Aabb
aB	AaBB	AaBb	aaBB	aaBb
ab	AaBb	Aabb	aaBb	aabb

9 : 3 : 3 : 1

	RY	Ry	rY	ry
RY	RRYY	RRYy	RrYY	RrYy
Ry	RRYy	RRyy	RrYy	Rryy
rY	RrYY	RrYy	RrYy	Rryy
ry	RrYy	Rryy	rrYy	rryy

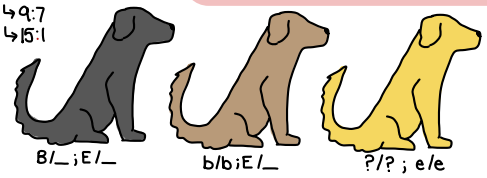
Assumptions of 9:3:3:1 Ratio:

- Both the product rule and the Punnett Square approaches showed that a 9:3:3:1 phenotypic ratio is expected among the progeny of a dihybrid cross, such as Mendel's RrYy x RrYy. In making these expectations, we assumed:
  1. Both loci assort independently;
  2. One allele at each locus is completely dominant; and
  3. Each of four possible phenotypes can be distinguished unambiguously, w/ no interactions b/w the two genes that would alter the phenotypes
- Deviations from the 9:3:3:1 phenotypic ratio may indicate that one or more of the above conditions is not met.
  - ex: Linkage of the two loci result in a distortion of the ratios expected from independent assortment.
- Also, if complete dominance is lacking
  - ex: co-dominance or incomplete dominance, then the ratios will also be distorted.
- Finally, if there is an interaction b/w the two loci such that the four classes cannot be distinguished the ratio will also deviate from 9:3:3:1
- Modified ratios in the progeny of a dihybrid cross can therefore reveal useful information about the genes being investigated. Such interactions lead to MODIFIED MENDELIAN RATIOS

Epistasis & Other Gene Interactions

- Some dihybrid crosses produce a phenotypic ratio that differs from the typical 9:3:3:1
  - These include:
    - ↳ 9:3:4
    - ↳ 12:3:1
    - ↳ 9:7
    - ↳ 15:1

Note: Each of these modified ratios can be obtained by summing one or more of the 9:3:3:1 classes expected from our original dihybrid cross.



B/_ ; E/_ b/b ; E/_ ?/? ; e/e

Recessive Epistasis

- Epistasis (which means "standing upon") occurs when the phenotype of one locus masks, or prevents, the phenotypic expression of another locus.
  - Thus, following a dihybrid cross, fewer than the typical four phenotypic classes will be observed with epistasis.
- In the absence of epistasis, there are four phenotypic classes among the progeny of a dihybrid cross
- The four phenotypic classes correspond to the genotypes:
  1. A_B_
  2. A_bb
  3. aaB_
  4. aabb
- If either of the singly homozygous recessive genotypes (ex: A_bb or aaB_) has the same phenotype as the double homozygous recessive (aabb), then a 9:3:4 phenotypic ratio will be obtained
  - ex: in the Labrador Retriever breed of dogs the B locus encodes a gene for an important step in the production of melanin.

The dominant allele, B is more efficient at pigment production than the recessive b allele, thus B_ hair appears black, & bb hair appears brown.

A second locus, which we will call E, controls the deposition of melanin in hairs.
At least one functional E allele is required to deposit any pigment whether it is black or brown.

Thus all retrievers that are ee fail to deposit any melanine (so they appear yellow-white), regardless of the gene type at the B locus

The ee genotype is therefore said to be epistatic to both the B & b alleles, since the homozygous ee phenotype masks the phenotype of the B locus.

The B/b locus is said to be hypostatic to the ee genotype.
Because the masking allele is, in this case, recessive.
This is called recessive epistasis.

	EB	Eb	eB	eb
EB	EEBB	EEBb	EeBB	EeBb
Eb	EEBb	EEbb	EeBb	Eebb
eB	EeBB	EeBb	eeBb	eeBb
eb	EeBb	Eebb	eeBb	eebb

Duplicate Gene Action

When a dihybrid cross produces progeny in two phenotypic classes in a 15:1 ratio, this can be because the two loci's gene products have the same (redundant) functions within the sam biological pathway.
ex: Wheat shows this duplicate gene action.

The biosynthesis of red pigment near the surface of wheat seeds involves many genes, two of which we will label A & B.

Normal, red colouration of the wheat seeds is maintained if function of either of these genes is lost in a homozygous mutant (ex: either aaB_ or A_bb)

Only the doubly recessive mutant (aabb), which lacks function of both genes shows a phenotype that differs from that produced by any of the other genotypes

A reasonable interpretation of this result is that both genes encode the same biological function, and either one alone is sufficient for the normal activity of that pathway

	AB	Ab	aB	ab
AB	AABB	AABb	AaBB	AaBb
Ab	AABb	AAbb	AaBb	Aabb
aB	AaBB	AaBb	aaBB	aaBb
ab	AaBb	Aabb	aaBb	aabb

Dominant Epistasis

- In some cases, a dominant allele at one locus may mask the phenotype of a second locus.
  - This is called DOMINANT EPISTASIS.
- This produces a segregation ratio of 12:3:1, which can be viewed as a modification of the 9:3:3:1 ratio.
  - Here the A_B_ class is combined with one of the other genotypic classes (9+3) that contains a dominant allele.
    - ↳ ex: 12:3:1 segregation ratio is fruit colour in some types of squash

Alleles of a locus that we will call B produce either
yellow (B_) fruit
or
green (bb) fruit

However, in the presence of a dominant allele at a second locus that we call A, no pigment is produced at all, & fruit are white.

The dominant A allele, is therefor, epistatic at BOTH B & bb combinations

One possible biological interpretation of this segregation pattern, is that the function of the A allele somehow blocks an early stage of pigment synthesis before either yellow or green pigment are produced

	AB	Ab	aB	ab
AB	AABB	AABb	AaBB	AaBb
Ab	AABb	AAbb	AaBb	Aabb
aB	AaBB	AaBb	aaBB	aaBb
ab	AaBb	Aabb	aaBb	aabb

Complementary Gene Action

- The progeny of a dihybrid cross may produce just two phenotypic classes in an approximately 9:7 ratio.
- An interpertation of this ratio is that the loss of function of either
- A or B genes has the same phenotypes at the loss of function of both genes.
  - This is due to complementary gene action; meaning the functions of both genes work together to produce a final product.
  - Ex: Consider a simple biochemical pathway in which a colourless substrate is converted by the action of gene A to another colourless product, which is then converted by the action of gene B to a visible pigment

a) colourless compound #1 —Gene A→ colourless compound #2 —Gene B→ Purple Pigment

b) Two subunits of one enzyme
w1+ w2+
white precursor → Purple end pigment

c) One transcript factor & one enzyme
w1+ w2+
white precursor → Purple end product

- Loss of function of either A or B, or both, will have the same result—no pigment production.
  - Thus A_bb, aaB_ & aabb will all be colourless, while only A_B_ genotypes will produce pigmented product.
- The modified 9:7 ratio may, therefore, be obtained when two genes act together in the same biochemical pathway, and when their loss of function phenotypes are indistinguishable from each other or from the loss of both genes.
- There are also other possible biochemical explanations for complementary gene action

	AB	Ab	aB	ab
AB	AABB	AABb	AaBB	AaBb
Ab	AABb	AAbb	AaBb	Aabb
aB	AaBB	AaBb	aaBB	aaBb
ab	AaBb	Aabb	aaBb	aabb

Cont'd... Epistasis & Other Gene Interactions

Genetic Suppression & Enhancement

- A suppressor mutation is a type of mutation that usually had no phenotype of its own, but act to suppress (makes more wildtype, less mutant) the phenotypic expression of another mutation that already exists in an organism.
- On the other hand, enhancer mutations have the opposite effects of suppressor mutations.
- They make the phenotype more mutant & less wild type (enhance the mutant phenotype)
  - Ex If a fly has a whitemottled (wm) phenotype, it can be supressed to look more like white+ phenotype by a dominant suppressor mutations (S-) or Enhanced to look more like white- by a dominant enhancer mutation (E-)

NOTE: The wm allele is recessive to white (w+) but dominant to white (w-)

- The suppressor mutation can be within the original gene, itself (intragenic), or outside the gene, at some other gene elsewhere in the genome (extragenic)
  - Ex: a Frameshift mutation caused by a deletion in a gene can be reverted, or suppressed, by an insertion in the same gene to restore the original reading frame (intragenic suppressor mutation)
- A case of an extragenic suppressor mutation, on the other hand, a can occur when a mutant phenotype caused by mutation in gene A is suppressed by a mutation in gene B
- In extragenic suppressor mutation, there are two types of suppressor mutations:
  1. Dominant suppression
  2. Recessive suppression

Modifications Summary:

Ratio	Description	Interaction
9:3:3:1	Complete dominance at both gene pairs; new phenotypes result from interaction between dominant alleles, as well as from interaction between both homozygous recessives	None (Independent Assortment)
9:4:3	Complete dominance at both gene pairs; however, when one gene is homozygous recessive, it masks the phenotype of the other gene	Recessive epistasis
9:7	Complete dominance at both gene pairs, however, when either gene is homozygous recessive, it masks the effect of the other gene	Duplicate recessive epistasis
12:3:1	Complete dominance at both gene pairs; however, when one gene is dominant, it masks the phenotype of the other gene	Dominant epistasis
15:1	Complete dominance at both gene pairs; however, when either gene is dominant, it masks the effects of the other gene	Duplicate dominant epistasis
13:3	Complete dominance at both gene pairs; however, when either gene is dominant, it masks the effects of the other gene	Dominant and recessive epistasis
9:6:1	Complete dominance at both gene pairs; however, when either gene is domiant, it masks the effects of other gene	Duplicate interaction

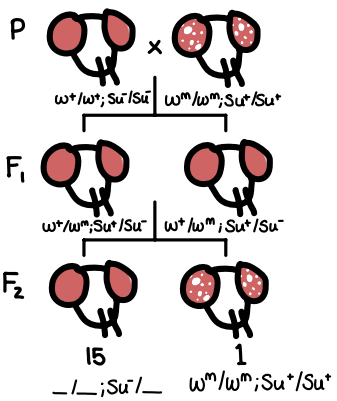
Dominant Suppression

- In dominant suppression, the mutant suppressor allele is dominant to the wild type suppressor allele.
- Therefore, one mutant suppressor allele is sufficient to supress the mutant phenotype.
  - Ex: Su gene represents the suppressor gene.

Flies that have at least one Su- allele, even though they have homozygous recessive wm/wm genotype, will show a wild-type (w+) phenotype.

A fly will have wm phenotype only it it has homozygous recessive Su+/Su+ genotype.

If w+/wmottled; Su+/Su- flies are crossed together, the ratio of white+ (wild type) to whitemottled (mutant) would be 15:1



	AB	Ab	aB	ab
AB	AABB	AABb	AaBB	AaBb
Ab	AABb	AAbb	AaBb	Aabb
aB	AaBB	AaBb	aaBB	aaBb
ab	AaBb	Aabb	aaBb	aabb

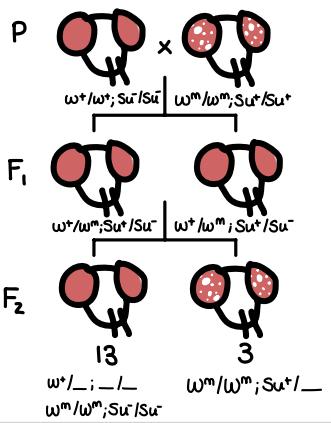
Recessive Suppression

- On the other hand, in recessive suppression, the mutant suppressor allele is recessive to the wild type suppressor allele.
- Therefore, two of the mutant alleles are needed to suppress the wm (mottled) phenotype.
  - Ex: In flies that have at least one w+ allele will show a wild-type phenotype.

Also flies that have su-/su- alleles will have wildtype phenotype since two mutant alleles can supress the white gene mutation.

On the other hand, flies that have the wm/wm alleles will have mottled phenotype unless they have homozygous su- alleles.

If w+/wmottled, Su+/Su- flies are crossed together, the ratio of white+ (wildtype) to whitemottled (mutant) would be 13:3



	AB	Ab	aB	ab
AB	AABB	AABb	AaBB	AaBb
Ab	AABb	AAbb	AaBb	Aabb
aB	AaBB	AaBb	aaBB	aaBb
ab	AaBb	Aabb	aaBb	aabb

Polygenic Inheritance

Continuous Variation

Most of the phenotypic traits commonly used in introductory genetics are qualitative.

This means phenotype exists in only two (or possibly a few more) discrete, alternative forms, such as purple or white flowers, or red or white eyes.

Thes qualitative traits are therefore said to exhibit discrete variation.

On the other hand, many interesting & important traits exhibit continuous variation meaning they exhibit a continuous range of phenotypes that are usually measured qualitatively such as intelligence, body mass, blood pressure in animals (including humans), and yeild, water use, or vitamin content in crops.

Traits w/ continuous variation are often complex & do not show the simple mendelian segregation ratios (3:1) observed w/ some qualitative traits.

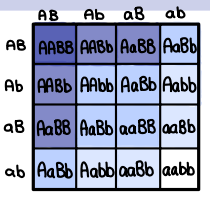
Many complex traits are heavily influenced by the environment; nevertheless, complex traits often have a component that is heritable, and which must therefore involve one or more genes.

If the number of phenotypic classes is sufficiently large (as w/ 3 or more loci) individual classes may become indistinguishable (particularly when environmental effects are included) and the phenotype appears as a continuous

Thus, quantitative traits are sometimes called polygenic traits because it is assumed that their phenotypes are controlled by the combined activity of many genes

How can genes, which are inherited (in the case of a diploid) as at most two variants each, explain the wide range of continuous variation observed for many traits?

The lack of an immediatly obvious explanation to this question was one of the early objections to Mendel's explanation of the mechanisms of heredity. However, upon further consideration, it becomes clear that the more loci that contribute to the trait, the more phenotypic classes may be observed for that trait



	A	a
A	AA	Aa
a	Aa	aa

NOTE: This does not imply that each of the individual genes has an equal influence on a polygenic trait - some may have a major effect while others only minor. Furthermore, any single gene may influence more than one trait whereas these traits are quantitative or qualitative traits

Environmental Factors

- The phenotypes described thus far, have a nearly perfect correlation w/ their associated genotypes.
- In other words, an individual w/ a particular genotype always has the expected phenotype.
- However, most phenotypes are not determined entirely by genotype alone.
- Instead they are determined by an interaction b/w genotype & environmental factors & can be determined conceptualized in the following relationship:

$$\text{Genotype} + \text{Environment} \longrightarrow \text{Phenotype} \quad (G+E \rightarrow P)$$

OR

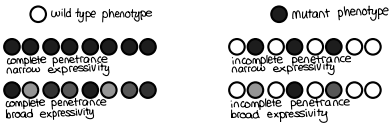
$$\text{Genotype} + \text{Environment} + \text{Interaction GE} \longrightarrow \text{Phenotype} \quad (G+E+IGE \rightarrow P)$$

*GE = Genetics & Environment

- This interaction is especially relevant in the study of economically important phenotypes, such as human diseases or agricultural productivity.
  Ex A particular genotype may be pre-dispose an individual to cancer, but cancer may only develop if the individual exposed to certain DNA damaging chemicals/carcinogens.
- Therefor, not all individuals w/ the particular genotypes will develope the cancer phenotype, only those who experience a particular environment.
- The terms penetrance & expressivity are also useful to describe the relationship b/w certain genotypes & their phenotypes

Penetrance:

- Penetrance is the proportion of individuals w/ a particular genotype that display a corresponding phenotype
- It is usually expressed as a percentage of the population.
- Because all pea plants are homozygous for the allele for white flowers, this genotype is completely (100%) penetrant
- In contrast many human genetic diseases are incompletely penetrant, since not all individuals w/ the disease genotype develop symptoms associated w/ the disease (less than 100%)



Expressivity

- Expressivity describes the variability in mutant phenotypes observed in individuals w/ a particular phenotype
- Many human genetic diseases provide examples of broad expressivity, since individuals w/ the same genotypes may vary greatly in the severity of their symptoms.
- Incomplete penetrance & broad expressivity are due to random chance, non-genetic (environmental), and genetic factors (mutations in other genes)

Factors Causing Deviations From Mendelian Phenotypic Ratios

There are other factors that affect an organisms phenotype and thus appear to alter Mendelian inheritance:

1. Genetic Heterogeneity: There is more than one gene or genetic mechanism that can produce the same phenotype
2. Polygenic Determination: One phenotypic trait is controlled by multiple genes
3. Phenocopy: Organisms that do not have the genotype for trait A can also express trait A due to environmental conditions; they do not have the same genotype but the environment simply "copies" the genetic phenotype
4. Incomplete Penetrance: Even though an organism possesses the genotype for trait A, it might not be expressed w/ 100% effect
5. Certain genotypes show a survival rate that is less than 100%.
   ex: genotypes that cause death, recessive lethal mutations, at the embryo or larval stages will be underrepresented when adult flies are counted