Chapter 5
Gene Interactions

Figure 5-1
Coat color in mammals is an example of a phenotypic trait that is controlled by more than one locus and the alleles at these loci can interact to alter the expected Mendelian ratios. (Flickr-David Blaikie- CC BY 2.0)

Introduction

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 between genes that affect the phenotype. Understanding these interactions is very useful for both basic and applied research. Before discussing these interactions, we will first revisit Mendelian inheritance for two loci.

A Mendelian Dihybrid Crosses

A.1 Mendel's second law (a quick review)

To analyze the segregation of two traits (e.g. 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 and round, and which were also **dihybrids**; they carried two alleles at each of two loci (**Figure 5-2**).

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 within each phenotypic class of the other trait (Figure 5-2). Using the product law, we would therefore predict that if ¾ of the progeny were green, and ¾ of the progeny were round, then ¾ × ¾ = 9/16 of the progeny would be both round and green. Likewise, ¾ × ¼ = 3/16 of the progeny would be both round and yellow, and so on. By applying the product

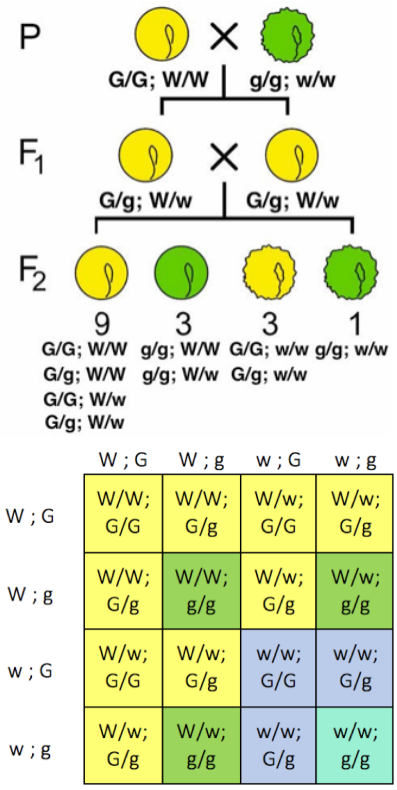

Figure 5-2
Pure-breeding lines are crossed to produce dihybrids in the F_1 generation. The cross of these particular dihybrids produces four phenotypic classes.

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rule to all of 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. Indeed, 9:3:3:1 is very close to the ratio Mendel observed in his studies of dihybrid crosses, leading him to state his Second Law, the **Law of Independent Assortment**, which we now express as follows: two loci assort independently of each other during gamete formation.

A.2 Assumptions of the 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 *R/r;Y/y* × *R/r;Y/y*. In making these expectations, we assumed that:

(1) both loci assort independently (not the semicolon);

(2) one allele at each locus is completely dominant; and

(3) each of four possible phenotypes can be distinguished unambiguously, with no interactions between 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 has not been met. For example, Linkage of the two loci results in a distortion of the ratios expected from independent assortment. Also, if complete dominance is lacking (e.g. co-dominance or incomplete dominance) then the ratios will also be distorted. Finally, it there is an interaction between the two loci such that the four classes cannot be distinguished (which is the topic under consideration in this chapter) 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**.

B Epistasis and 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, or 15:1. Note that 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. In the following sections, we will look at some modified phenotypic ratios obtained from dihybrid crosses and what they might tell us about the interactions between the genes involved.

B.1 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. As we have already discussed, 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: *A/-;B/-, A/-;b/b, a/a;B/-,* and *a/a;b/b*. If either of the singly homozygous recessive genotypes (i.e. *A/-;b/b* or *a/a;B/-*) has the same phenotype as the double homozygous recessive (*a/a;b/b*), then a **9:3:4** phenotypic ratio will be obtained.

For example, in the Labrador Retriever breed of dogs (**Figure 5-3**), 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, and *b/b* hair appears brown. A second locus, which we will call *Y*, controls the deposition of melanin in the hairs. At least one functional *Y* allele is required to deposit any

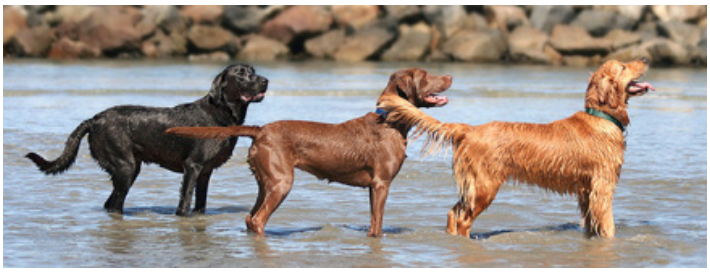

Figure 5-3

Retrievers with different coat colors: (from left to right) black, chocolate, yellow: an example of recessive epistasis phenotypes.

(Flickr- Pirate Scott - CC BY-NC 2.0)

	Y/B	Y/b	y/B	y/b
Y/B	Y/Y;B/B	Y/Y;B/b	Y/y;B/B	Y/y;B/b
Y/b	Y/Y;B/b	Y/Y;b/b	Y/y;B/b	Y/y;b/b
y/B	Y/y;B/B	Y/y;B/b	y/y;B/B	y/y;B/b
y/b	Y/y;B/b	Y/y;b/b	y/y;B/b	y/y;b/b

Figure 5-4

Genotypes and phenotypes among the progeny of a dihybrid cross of Labrador Retrievers heterozygous for two loci affecting coat color. The phenotypes of the progeny are indicated by the shading of the cells in the table: black coat (black, *Y/-;B/-*); chocolate coat (brown, *Y/-;b/b*); yellow coat (yellow, *y/y;B/-* or *y/y;b/b*).

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pigment, whether it is black or brown. Thus, all retrievers that are *y/y* fail to deposit any melanin (and so appear pale yellow-white), regardless of the genotype at the *B* locus (**Figure 5-3**, right side).

The *y/y* genotype is therefore said to be **epistatic** to both the B and b alleles, since the homozygous *y/y* phenotype masks the phenotype of the *B* locus. The *B/b* locus is said to be **hypostatic** to the *y/y* genotype. A graphic showing all the possible progeny genotypes and their phenotypes is shown in **Figure 5-4**.

In some cases, a dominant allele at one locus may mask the phenotype of a second locus. This produces a segregation ratio of **12:3:1**, which can be viewed as a modification of the 9:3:3:1 ratio in which the *A/-;B/-* class is combined with one of the other genotypic classes (9+3) that contains a dominant allele. One of the best known examples of a 12:3:1 segregation ratio is fruit color in some types of squash (**Figure 5-5**). Alleles of a locus that we will call *B* produce either yellow (*B*/-) or green (*b/b*) fruit. However, in the presence of a dominant allele at a second locus that we call *A*, no pigment is produced at all, and fruit are white. The dominant *A* allele is therefore epistatic to both *B* and *b/b* combinations (**Figure 5-6**). 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 pigments are produced.

Figure 5-5
Green, yellow, and white fruits of squash.

(Flickr-Unknown-CC BY-NC 3.0)

	A/B	A/b	a/B	a/b
A/B	A/A;B/B	A/A;B/b	A/a;B/B	A/a;B/b
A/b	A/A;B/b	A/A;b/b	A/a;B/b	A/a;b/b
a/B	A/a;B/B	A/a;B/b	a/a;B/B	a/a;B/b
a/b	A/a;B/b	A/a;b/b	a/a;B/b	a/a;b/b

Figure 5-6
Genotypes and phenotypes among the progeny of a dihybrid cross of squash plants heterozygous for two loci affecting fruit color.

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B.2 Duplicate Gene Action

When a dihybrid cross produces progeny in two phenotypic classes in a 15:1 ratio, this can be because the proteins from each different gene have the same (redundant) functions within the same biological pathway. With yet another pigmentation pathway example, wheat shows this form of epistasis. The biosynthesis of red pigment near the surface of wheat seeds (**Figure 5-7**) involves many genes, two of which we will label *A* and *B*. Normal, red coloration of the wheat seeds is maintained if function of either of these genes is lost in a homozygous mutant (e.g. in either *a/a;B/-* or *A/-;b/b*). Only the doubly recessive mutant (*a/a;b/b*), which lacks function of both genes, shows a phenotype that differs from that produced by any of the other genotypes (**Figure 5-8**). 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.

Figure 5-7
Red (left) and white (right) wheat seeds.

(cropwatch.unl.edu)

	A/B	A/b	a/B	a/b
A/B	A/A;B/B	A/A;B/b	A/a;B/B	A/a;B/b
A/b	A/A;B/b	A/A;b/b	A/a;B/b	A/a;b/b
a/B	A/a;B/B	A/a;B/b	a/a;B/B	a/a;B/b
a/b	A/a;B/b	A/a;b/b	a/a;B/b	a/a;b/b

Figure 5-8
Genotypes and phenotypes among the progeny of a dihybrid cross of a wheat plants heterozygous for two loci affecting seed color.

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B.3 Complementary Gene Action

The progeny of a dihybrid cross may produce just two phenotypic classes, in an approximately **9:7** ratio. An interpretation of this ratio is that the loss of function of either A or B gene function has the same phenotype as the loss of function of both genes. For example, consider a simple biochemical pathway in which a colorless substrate is converted by the action of gene A to another colorless product, which is then converted by the action of gene B to a visible pigment (**Figure 5-9** next page).

Loss of function of either A or B, or both, will have the same result: no pigment production. Thus *A/-;b/b*,

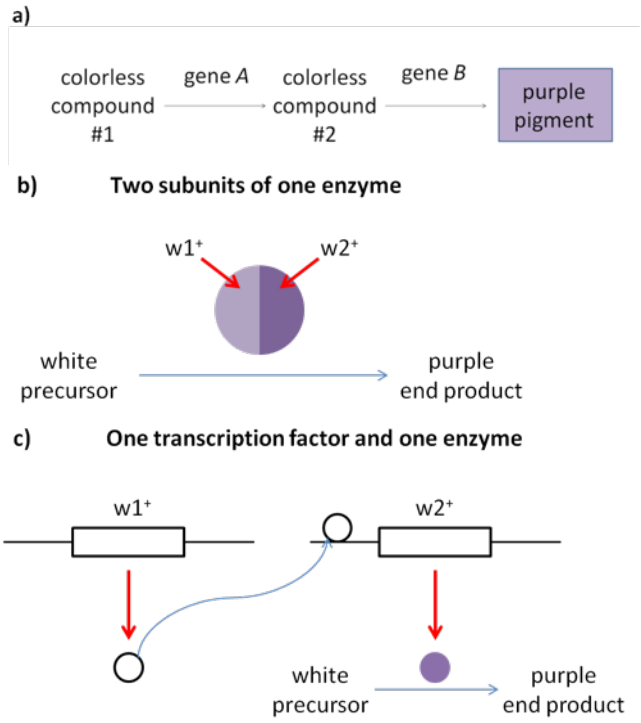

Figure 5-9

a) A simplified biochemical pathway showing complementary gene action of A and B. Note that in this case, the same phenotypic ratios would be obtained if gene B acted before gene A in the pathway.

b) biochemical pathway showing two subunits of one enzyme

c) biochemical pathway showing one transcription factor and one enzyme

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a/a;B/-, and *a/a;b/b* will all be colorless, while only *A/-;B/-* genotypes will produce pigmented product (**Figure 5-10**). 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.

	A/B	A/b	a/B	a/b
A/B	A/A;B/B	A/A;B/b	A/a;B/B	A/a;B/b
A/b	A/A;B/b	A/A;b/b	A/a;B/b	A/a;b/b
a/B	A/a;B/B	A/a;B/b	a/a;B/B	a/a;B/b
a/b	A/a;B/b	A/a;b/b	a/a;B/b	a/a;b/b

Figure 5-10

Genotypes and phenotypes among the progeny of a dihybrid cross of a hypothetical plant heterozygous for two loci affecting flower color.

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C GENETIC SUPPRESSION: RECESSIVE AND DOMINANT SUPPRESSION

A **Suppressor mutation** is a type of mutation that suppresses the phenotypic expression of another mutation that already exists, which results in a more wild type (less mutant) phenotype. On the other hand, **enhancer mutations** have the opposite effect of suppressor mutations as they make the phenotype more mutant (enhance the mutant phenotype).

For example, if a fly has a mottled (whi^m) phenotype, it can be suppressed to look more like whi^+ phenotype by a dominant suppressor mutation, or enhanced to look more like whi^- by a dominant enhancer mutation (whi^-/whi^- whi^m/whi^m $whi^+/-$ or whi^m/whi^-; see **Figure 5-11**).

Note that whi^m is recessive to whi^+ but dominant to whi^-. This is an example of an **allelic series** (more than one allele of a gene can be in play. Another example is the A/B/O blood type series of alleles).

Figure 5-11

Mutation in the *white* gene impacts the pigmentation in *Drosophila* eyes. Note that whi^m (for $white^{mottled}$) is recessive to whi^+ and dominant to whi^-.

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The suppressor mutation can happen within the original gene itself (**intragenic**) or outside the gene, at some other gene elsewhere in the genome (**extragenic**). For example, a frameshift mutation caused by a deletion in gene A can be reverted by an insertion in the same gene to regain the reading frame (intragenic suppressor mutation). On the other hand in extragenic suppressor mutation, a defect caused by mutation in gene A can be suppressed by a mutation in gene B. In extragenic suppressor mutation, there are two types of suppressor mutations: (1) **dominant suppression** and (2) **recessive suppression.**

C.1 Dominant suppression

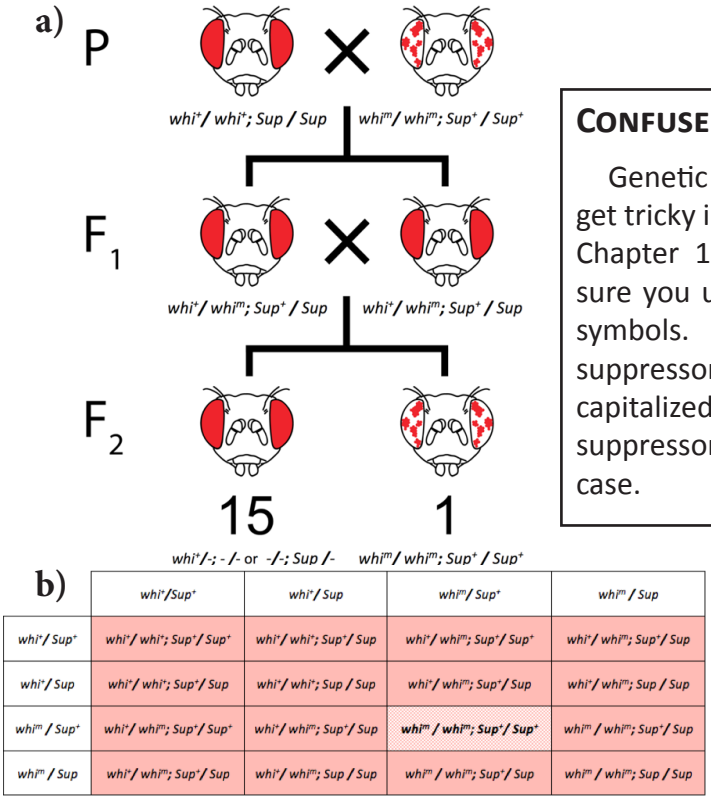
In **dominant suppression**, the mutant suppressor allele (*Sup*) is dominant to the wild type suppressor allele (*Sup*$^+$). Therefore, one mutant suppressor allele is sufficient to suppress the mutant phenotype. For example, in **Figure 5-12**, the *Sup* gene represents the suppressor gene. Flies that have at least one *Sup* allele, even though they have a homozygous recessive *whi*^{m}/*whi*^{m} genotype, will show a wild-type (*whi*$^+$) phenotype. A fly will have *whi*^{m} phenotype only if it has homozygous recessive *Sup*$^+$/*Sup*$^+$ genotype. *If whi*$^+$/*whi*^{m};*Sup*$^+$/*Sup* flies are crossed together, the ratio of *whi*$^+$/-(wild type) to *whi*^{m} /*whi*^{m} (mutant) would be 15:1.

C.2 Recessive suppression

On the other hand, in **recessive suppression**, the mutant suppressor allele (*rsp*) is recessive to the wild type suppressor allele (*rsp*$^+$). Therefore, two of the mutant alleles are needed to suppress the *whi*^{m} (mottled) phenotype. For example, in **Figure 5-13**, flies that have at least one *whi*$^+$ allele will show a wild-type phenotype. Also, flies that homozygous for *rsp* will have wildtype phenotype since only two mutant alleles can suppress the *white* gene mutation. On the other hand, flies that have the *whi*^{m}/*whi*^{m} alleles will have mottled phenotype unless they have homozygous *rsp* alleles. If *whi*$^+$/*whi*^{m};*rsp*$^+$/*rsp* flies are crossed, the ratio of *whi*$^+$/- (wild type) to *whi*^{m}/ *whi*^{m} (mutant) would be 13:3.

Confused?

Genetic problems can get tricky in a hurry. Check Chapter 1 again to make sure you understand gene symbols. The dominant suppressor, *Sup* is capitalized; the recessive suppressor *rsp* is all lower case.



b)

	whi+/Sup+	whi+/ Sup	whim/ Sup+	whim / Sup
whi+/ Sup+	whi+/ whi+; Sup+/ Sup+	whi+/ whi+; Sup+/ Sup	whi+/ whim; Sup+/ Sup+	whi+/ whim; Sup+/ Sup
whi+/ Sup	whi+/ whi+; Sup+/ Sup	whi+/ whi+; Sup / Sup	whi+/ whim; Sup+/ Sup	whi+/ whim; Sup / Sup
whim / Sup+	whi+/ whim; Sup+/ Sup+	whi+/ whim; Sup+/ Sup	**whim / whim; Sup+/ Sup+**	whim / whim; Sup+/ Sup
whim / Sup	whi+/ whim; Sup+/ Sup	whi+/ whim; Sup / Sup	whim / whim; Sup+/ Sup	whim / whim; Sup / Sup

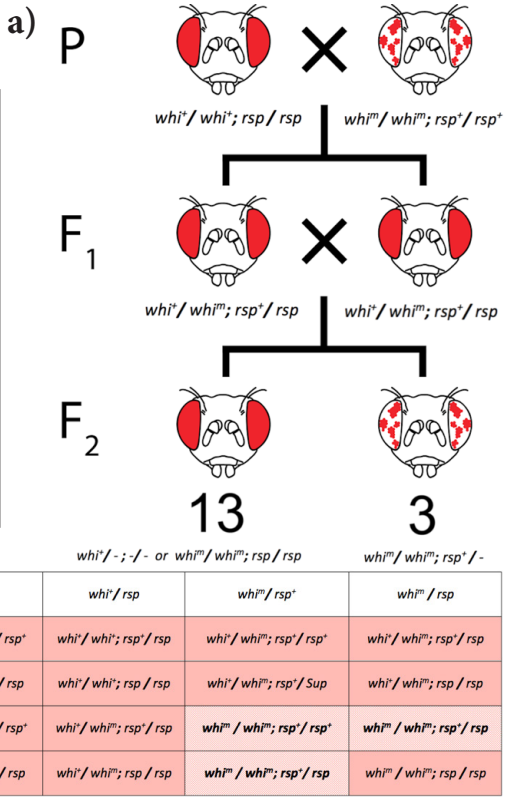
c)

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

Figure 5-12
Drosophila cross and its Punnett square showing the effects of dominant suppression of the *Sup* gene on the *whi* gene. Note that a dash(-) = indicates any allele for that locus.

a) crosses and genotypes; b) Punnett square with proper gene names; c) simplified Punnett square where A=*whi*$^+$, a=*whi*, B=*Sup*$^+$, and b=*Sup*

(Image-Kang, modified by Nickle-CC BY-NC 3.0; Table – Nickle – CC BY-SA 3.0)



b)

	whi+/ rsp+	whi+/ rsp	whim/ rsp+	whim / rsp
whi+/ rsp+	whi+/ whi+; rsp+/ rsp+	whi+/ whi+; rsp+/ rsp	whi+/ whim; rsp+/ rsp+	whi+/ whim; rsp+/ rsp
whi+/ rsp	whi+/ whi+; rsp+/ rsp	whi+/ whi+; rsp / rsp	whi+/ whim; rsp+/ Sup	whi+/ whim; rsp / rsp
whim / rsp+	whi+/ whim; rsp+/ rsp+	whi+/ whim; rsp+/ rsp	**whim / whim; rsp+/ rsp+**	**whim / whim; rsp+/ rsp**
whim / rsp	whi+/ whim; rsp+/ rsp	whi+/ whim; rsp / rsp	**whim / whim; rsp+/ rsp**	whim / whim; rsp / rsp

c)

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

Figure 5-13
Drosophila cross and its Punnett square showing the effects of dominant suppression of the *rsp* gene on the *whi* gene. Note that a dash(-) = indicates any allele for that locus.

a) crosses and genotypes; b) Punnett square with proper gene names; c) simplified Punnett square where A=*whi*□, a=*whi*, B=*rsp*□, and b=*rsp*

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You've had an awful lot of interactions to consider! So far you've seen how the 9:3:3:1 ratios are altered by having a unique phenotype for each genotype. With no gene interaction, you should see 2^n phenotypes where n=# genes involved.

Also critical for this section is that the genes must be independently assorting. Genes that are close enough together on the same chromosome are "linked", and linkage always shows a shift in the ratios that differs from unlinked genes. See Chapters 3 (page 24), 9, and 10 for details.

Table 5-1 summarizes the different forms of epistasis and the ratios they produce for interacting, unlinked loci.

Table 5-1

Summary showing gene interactions and their genotypic (italic) and phenotypic (bold) ratios. Shading represents combined classes. Letters in italics represent alleles. Bolded letters refer to phenotypes. Where possible, the phenotype is given the same letter as the allele which is responsible for it. The names of the various forms of epistasis are provided, but for this course you need not memorize them. Just recognize how the 9:3:3:1 ratios are altered and be able to provide possible biochemical reasons for the alteration in ratio.

Fraction:	9	3	3	1	Ratio
Genotype:	*A/-;B/-*	*A/-;b/b*	*a/a;B/-*	*a/a;b/b*	
None	9 **A;B**	3 **A;b**	3 **a;B**	1 **a;b**	9:3:3:1
"Recessive" epistasis *a/a* influences *B* and *b* alleles	9 **A;B**	3 **A;b**	4 **a**		9:3:4
"Dominant" epistasis *A* influences *B* and *b* alleles	12 **A**		3 **a;B**	1 **a;b**	12:3:1
Duplicate Genes *Dominant alleles either gene A or B creates phenotype* **C**, otherwise **c**	15 **C**			1 **c**	15:1
Complementary Genes *a/a* and *b/b* are identical (phenotype **c**) but distinct from *A&B which gives phenotype* **C**	9 **C**	7 **c**			9:7
Recessive Suppression *a/a* influences *b/b*	9 **B**	3 **A;b**	4 **B**		13:3
Dominant Suppression *A* disables expression of *b/b*	15 **B**			1 **a;b**	15:1

D Example of Multiple Genes Affecting One Character (Polygenic Inheritance)

D.1 Continuous variation

Most of the phenotypic traits commonly used in introductory genetics are qualitative, meaning that the phenotype exists in only two (or possibly a few more) discrete, alternative forms, such as either purple or white flowers, or red or white eyes. These qualitative traits are therefore said to exhibit **discrete variation**. On the other hand, many interesting and important traits exhibit **continuous variation**; these exhibit a continuous range of phenotypes that are usually measured quantitatively, such as intelligence, body mass, blood pressure in animals (including humans), and yield, water use, or vitamin content in crops. Traits with continuous variation are often complex, and do not show the simple Mendelian segregation ratios (e.g. 3:1) observed with some qualitative traits. The environment also influences many complex traits. Nevertheless, complex traits can

often be shown to have a component that is heritable, and which must therefore involve one or more 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 immediately 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 trait, the more phenotypic classes may be observed for that trait (**Figure 5-14**).

If the number of phenotypic classes is sufficiently large (as with three or more loci), individual classes may become indistinguishable from each other (particularly when environmental effects are included), and the phenotype appears as a continuous variation (**Figure 5-15**). Thus, quantitative traits are sometimes called **polygenic traits**, because it is assumed that their phenotypes are controlled by the combined activity of many genes. Note that this does not imply that each of the individual genes has an equal influence on a polygenic trait – some may have major effect, while others only minor. Furthermore, any single gene may influence more than one trait, whether these traits are quantitative or qualitative traits.

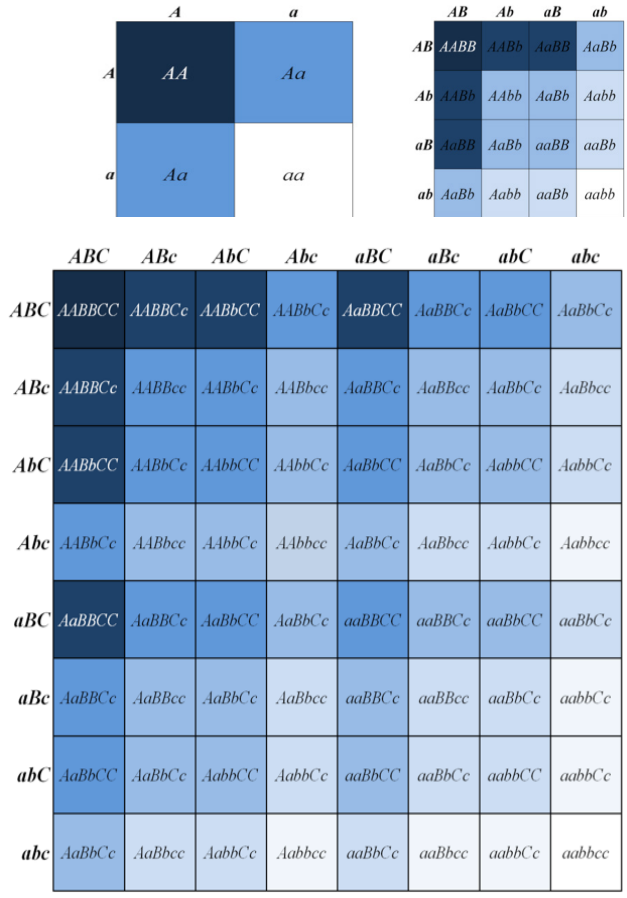

Figure 5-14

Punnett Squares for one, two, and three loci. We are using a simplified example of up to three semi-dominant genes, and in each case the effect on the phenotype is additive, meaning the more "upper case" alleles present, the stronger the phenotype. Comparison of the Punnett Squares and the associated phenotypes shows that under these conditions, the larger the number of genes that affect a trait, the more intermediate phenotypic classes that will be expected.

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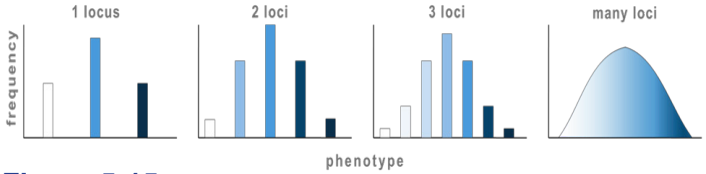

Figure 5-15

The more loci that affect a trait, the larger the number of phenotypic classes that can be expected. For some traits, the number of contributing loci is so large that the phenotypic classes blend together in apparently continuous variation.

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D.2 Cat fur genetics – (adapted from Christensen (2000) Genetics 155:999-1004)

Most aspects of the fur phenotypes of common cats can be explained by the action of just a few genes (Table 2). Other genes, not described here, may further modify these traits and account for the phenotypes seen in tabby cats and in more exotic breeds, such as Siamese.

For example, the X-linked ***Orange*** gene has two allelic forms. The O^O allele produces orange fur, while the O^B alleles produce non-orange (often black) fur. Note however, that because of X-chromosome inactivation the result is mosaicism in expression. In O^O / O^B female heterozygotes patches of black and orange are seen, which produces the tortoise shell pattern (**Figure 5-16 on page 46** A,B). This is a rare example of **codominance** since the phenotype of both alleles can be seen. Note that the cat in part A has short fur compared to the cat in part B; recessive alleles at an independent locus (L/l) produce long (*l/l*) rather than short (*L/-*) fur.

Alleles of the ***dilute*** gene affect the intensity of pigmentation, regardless of whether that pigmentation is due to black or orange pigment. Part C shows a black cat with at least one dominant allele of *dilute* (*D/-*), in contrast to the cat in D, which is grey rather than black, because it has the *d/d* genotype.

Epistasis is demonstrated by an allele of only one of

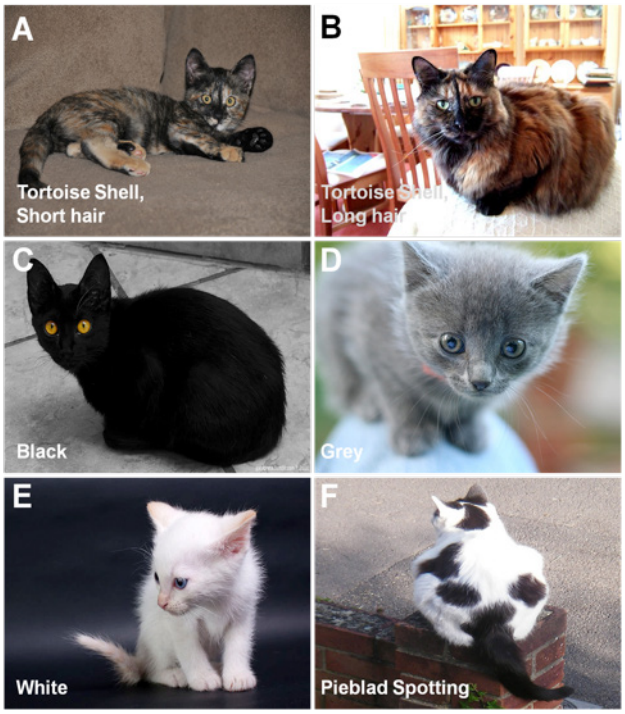


Figure 5-16

Representatives of various fur phenotypes in cats. Tortoise shell (A,B) pigmentation in cats with short (A) and long (B) fur; black (C) and grey (D) cats that differ in genotype at the dilute locus. The pure white pattern (E) is distinct from piebald spotting (F). A: (Flickr-Bill Kuffrey-CC BY 2.0), B: (Wikipedia-Dieter Simon-PD), C: (Flickr-atilave-lo-CC BY 2.0), D: (Flickr-Waldo Jaquith-CC BY-SA 2.0), E: (Wikipedia-Valerius Geng-CC BY-SA 3.0), F: (Flickr-Denni Schnapp-CC BY-NC-SA 2.0) *Changes: Letters and descriptions were added to the pictures.

Table 5-2

Summary of simplified cat fur phenotypes and genotypes.

Trait	Phenotype	Genotype	Comments
fur length	short	*L/L* or *L/l*	*L* is completely dominant
	long	*l/l*	
all white fur (non-albino)	100% white fur	*W/W* or *W/w*	If the cat has red eyes it is albino, not *W/-*. *W* is epistatic to all other fur color genes; if cat is *W/-*, can't infer genotypes for any other fur color genes.
	<100% white fur	*w/w*	
piebald spotting	> 50% white patches (but not 100%)	*S/S*	*S* is incompletely dominant and shows variable expressivity
	< 50% white patches	*S/s*	
	no white patches	*s/s*	
orange fur	all orange fur	X^O/X^O or X^O/Y	*O* is X-linked
	tortoise shell variegation	X^O/X^B	
	no orange fur (often black)	X^B/X^B or X^B/Y	
dilute pigmentation	pigmentation is intense	*D/D* or *D/d*	*D* is completely dominant
	pigmentation is dilute (e.g. gray rather than black; cream rather than orange; light brown rather than brown)	*d/d*	
tabby	tabby pattern	*A/A* or *A/a*	This is a simplification of the tabby phenotype, which involves multiple genes
	solid coloration	*a/a*	
sex	female	X/X	
	male	X/Y	

the genes in **Table 5-2**. One dominant allele of ***white masking*** (*W*) prevents normal development of melanocytes (pigment producing cells). Therefore, cats with genotype (*W/-*) will have entirely white fur regardless of the genotype at the *Orange* or *dilute* loci (part E). Although this locus produces a white colour, *W/-* is not the same as albinism, which is a much rarer phenotype caused by mutations in other genes. Albino cats can be distinguished by having red eyes, while *W/-* cats have eyes that are not red.

Piebald spotting is the occurrence of patches of white fur. These patches vary in size due to many reasons, including genotype. Homozygous cats with genotype *s/s* do not have any patches of white, while cats of genotype *S/s* and *S/S* do have patches of white, and the homozygotes tend to have a larger proportion of white fur than heterozygotes (part F). The combination of piebald spotting and tortoise shell patterning produce a **calico cat**, which has separate patches of orange, black, and white fur.

E Environmental Factors

The phenotypes described thus far have a nearly perfect correlation with their associated genotypes; in other words an individual with a particular genotype always has the expected phenotype. However, many (most?) phenotypes are not determined entirely by genotype alone. Instead, they are determined by an interaction between genotype and environmental factors and can be conceptualized in the following relationship:

Genotype + Environment

$$\Rightarrow \textbf{Phenotype (G + E} \Rightarrow \textbf{P)}$$

Or:

$$\textbf{Genotype + Environment + Interaction}_{GE}$$

$$\Rightarrow \textbf{Phenotype (G + E + I}_{GE} \Rightarrow \textbf{P)}$$

***GE = Genetics and Environment**

This interaction is especially relevant in the study of economically important phenotypes, such as human diseases or agricultural productivity. For example, a particular genotype may predispose an individual to cancer, but cancer may only develop if the individual is exposed to certain DNA-damaging chemicals or carcinogens. Therefore, not all individuals with the particular genotype will develop the cancer phenotype, only those who experience a particular environment.

F Penetrance and Expressivity

The terms penetrance and expressivity are also useful to describe the relationship between certain genotypes and their phenotypes.

F.1 Penetrance

Penetrance is the proportion of individuals with a particular genotype that display a corresponding phenotype (**Figure 18**). It is usually expressed as a percentage of the population. Because all pea plants that are homozygous for the allele for white flowers (e.g. *a/a in Chapter* 2 (page 13)) actually have white flowers, this genotype is completely (100%) penetrant. In contrast, many human genetic diseases are incompletely penetrant, since not all individuals with the disease genotype actually develop symptoms associated with the disease (less than 100%).

F.2 Expressivity

Expressivity describes the variability in mutant phenotypes observed in individuals with a particular phenotype (**Figure 5-17** and **Figure 5-18**). Many human genetic diseases provide examples of broad expressivity, since individuals with the same genotypes may vary greatly in the severity of their symptoms. Incomplete penetrance and broad expressivity are due to random chance, non-genetic (environmental), and genetic factors (mutations in other genes).

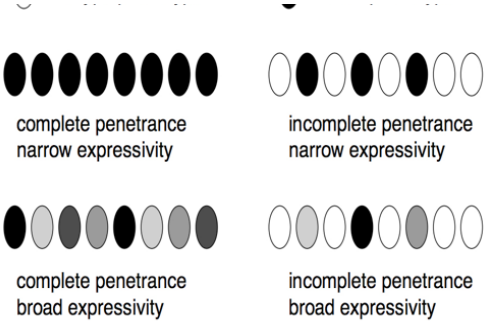


Figure 5-17

Relationship between penetrance and expressivity in eight individuals that all have a mutant genotype. Penetrance can be complete (all eight have the mutant phenotype) or incomplete (only some have the mutant phenotype). Amongst those individuals with the mutant phenotype the expressivity can be narrow (very little variation) to broad (lots of variation).

(Original-Locke-CC BY-NC 3.0)

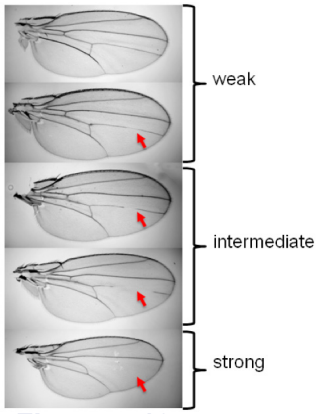


Figure 5-18

Mutations in wings of *Drosophila melanogaster* showing weak to strong expressivity.

(Original-J. Locke-CC; AN)

G Mendelian Phenotypic Ratios May Not Be As Expected

G.1 Other factors

There are other factors that that affects organism's 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 with 100% effect.

(5) Certain genotypes show a survival rate that is less than 100%. For example, genotypes that cause death, **recessive lethal mutations**, at the embryo or larval stage will be under-represented when adult flies are counted.

G.2 The X^2 test for goodness-of-fit

For a variety of reasons, the phenotypic ratios observed from real crosses rarely match the exact ratios expected based on a Punnett Square or other prediction techniques. There are many possible explanations for deviations from expected ratios. Sometimes these deviations are due to **sampling effects**, in other words, the random selection of a non-representative subset of individuals for observation.

A statistical procedure called the **chi-square** (χ^2) test can be used to help a geneticist decide whether the deviation between observed and expected ratios is due to sampling effects, or whether the difference is so large that some other explanation must be sought by re-examining the assumptions used to calculate the expected ratio. The procedure for performing a chi-square test is shown at http://tinyurl.com/chi2 .

Summary:

- Phenotype depends on the alleles that are present, their dominance relationships, and sometimes also interactions with the environment and other factors.
- The alleles of different loci are inherited independently of each other, unless they are genetically linked.
- Many important traits show continuous, rather than discrete variation. These are called quantitative traits.
- Many quantitative traits are influenced by a combination of environment and genetics.
- The expected phenotypic ratio of a dihybrid cross is 9:3:3:1, except in cases of linkage or gene interactions that modify this ratio.
- Modified ratios from 9:3:3:1 are seen in the case of recessive and dominant epistasis, duplicate genes, and complementary gene action. This usually indicates that the two genes interact within the same biological pathway.
- There are other factors that alter the expected Mendelian ratios.

Key terms:

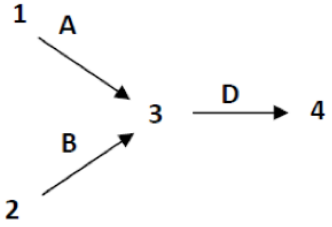
calico
continuous variation
dihybrid
dilute
discrete variation
duplicate gene action
expressivity
independent assortment
linkage
masking
Mendel's Second Law
modified Mendelian Ratios
penetrance
piebald spotting
polygenic traits
recessive epistasis
recessive lethal mutations
redundancy

Study Questions:

1. In the table to the right, match the mouse hair color phenotypes with the term from the list that best explains the observed phenotype, given the genotypes shown. In this case, the allele symbols do not imply anything about the dominance relationships between the alleles. List of terms: haplosufficiency, haplo-insufficiency, pleiotropy, incomplete dominance, co-dominance, incomplete penetrance, broad (variable) expressivity.

	A_1A_1	A_1A_2	A_2A_2
1	all hairs black	on the same individual: 50% of hairs are all black and 50% of hairs are all white	all hairs white
2	all hairs black	all hairs are the same shade of grey	all hairs white
3	all hairs black	all hairs black	50% of individuals have all white hairs and 50% of individuals have all black hairs
4	all hairs black	all hairs black	mice have no hair
5	all hairs black	all hairs white	all hairs white
6	all hairs black	all hairs black	all hairs white
7	all hairs black	all hairs black	hairs are a wide range of shades of grey

2. Answer questions 2-4 using the following biochemical pathway for fruit color. Assume all mutations (lower case allele symbols) are recessive, and that *either* precursor 1 or precursor 2 can be used to produce precursor 3. If the alleles for a particular gene are not listed in a genotype, you can assume that they are wild-type.



3. If 1 and 2 and 3 are all colorless, and 4 is red, what will be the phenotypes associated with the following genotypes?

a) *a/a*
b) *b/b*
c) *d/d*
d) *a/a;b/b*
e) *a/a;d/d*
f) *b/b;d/d*
g) *a/a;b/b;d/d*

h) What will be the phenotypic ratios among the offspring of a cross *A/a;B/b* × *A/a;B/b*?

i) What will be the phenotypic ratios among the offspring of a cross *B/b;D/d* × *B/b;D/d*?

j) What will be the phenotypic ratios among the offspring of a cross *A/a;D/d* × *A/a;D/d*?

4. If 1 and 2 are both colorless, and 3 is blue and 4 is red, what will be the phenotypes associated with the following genotypes?

   a) a/a
   b) b/b
   c) d/d
   d) a/a;b/b
   e) a/a;d/d
   f) b/b;d/d
   g) a/a;b/b;d/d
   h) What will be the phenotypic ratios among the offspring of a cross *A/a;B/b* × *A/a;B/b*?
   i) What will be the phenotypic ratios among the offspring of a cross *B/b;D/d* × *B/b;D/d*?
   j) What will be the phenotypic ratios among the offspring of a cross *A/a;D/d* × *A/a;D/d*?

5. If 1 is colorless, 2 is yellow and 3 is blue and 4 is red, what will be the phenotypes associated with the following genotypes?

   a) *a/a*
   b) b/b
   c) d/d
   d) a/a;b/b
   e) a/a;d/d
   f) b/b;d/d
   g) a/a;b/b;d/d
   h) What will be the phenotypic ratios among the offspring of a cross A/a;B/b × A/a;B/b?
   i) What will be the phenotypic ratios among the offspring of a cross B/b;D/d × B/b;D/d?
   j) What will be the phenotypic ratios among the offspring of a cross A/a;D/d × A/a;D/d?

6. Which of the situations in questions 2 – 4 demonstrate epistasis?

7. If the genotypes written within the Punnett Square are from the F_2 generation, what would be the phenotypes and genotypes of the F_1 and P generations for:

   a) Figure 5-4
   b) Figure 5-6
   c) Figure 5-8
   d) Figure 5-10

8. To better understand how genes control the development of three-dimensional structures, you conducted a mutant screen in *Arabidopsis* and identified a recessive point mutation allele of a single gene (*g*) that causes leaves to develop as narrow tubes rather than the broad flat surfaces that develop in wild-type (*G*). Allele *g* causes a complete loss of function. Now you want to identify more genes involved in the same process. Diagram a process you could use to identify other genes that interact with gene *g*. Show all of the possible genotypes that could arise in the F_1 generation.

9. With reference to question 7, if the recessive allele, *g* is mutated again to make allele *g**, what are the possible phenotypes of a homozygous *g* g** individual?

10. Again, in reference to question 8, what are the possible phenotypes of a homozygous *a/a;g/g* individual, where *a* is a recessive allele of a second gene? In each case, also specify the phenotypic ratios that would be observed among the F_1 progeny of a cross of *A/a;G/g* x *A/a;G/g*

11. Use the product rule to calculate the phenotypic ratios expected from a trihybrid cross. Assume independent assortment and no epistasis/gene interactions.