Gene Interactions and Modified Mendelian Ratios

2. Two types of interactions occur:
   a. Different genes control the same general trait, collectively producing a phenotype.
   b. One gene masks the expression of others (epistasis) and alters the phenotype.

3. Examples here are dihybrid, but in the “real world” larger numbers of genes are often involved in forming traits.

4. The molecular explanations offered here are currently hypothetical models, and await rigorous analysis using the tools of molecular biology.
Gene Interactions That Produce New Phenotypes

1. Nonallelic genes that affect the same characteristic may interact to give novel phenotypes, and often modified phenotypic ratios. Examples include:

   a. Comb shape in chickens, influenced by two gene loci to produce four different comb types. Each will breed true if parents are homozygous.

      i. In a cross between a homozygous rose-combed (R/R p/p) bird and a single-combed (r/r p/p) bird:

         (1) The F₁ (R/r p/p) will all have rose combs.
         (2) The F₂ will be 3 rose (R/– p/p) : 1 single (r/r p/p).
Gene Interactions That Produce New Phenotypes

ii. Similarly, pea comb (r/r P/P) is dominant over single (r/r p/p), with F₁ (r/r P/p) all showing pea combs, and a 3:1 ratio of pea to single in the F₂.

iii. Crossing true-breeding rose (R/R p/p) and pea (r/r P/P) results in:

1. An F₁ with all walnut combs (R/r P/p).
2. An F₂ showing a ratio of 9 walnut (R/– P/–) : 3 rose (R/– p/p) : 3 pea (r/r P/–) : 1 single (r/r p/p).

iv. These interactions fit the expected ratios for a Mendelian dihybrid cross. The molecular basis for each phenotype is unknown, but it appears that the dominant alleles R and P each produce a factor that modifies comb shape from single to a more complex form.
Figure 12.5
Four distinct comb shape phenotypes in chickens, resulting from all possible combinations of a dominant and a recessive allele at each of two gene loci. (a) Rose comb (R/– p/p). (b) Walnut comb (R/– P/–). (c) Pea comb (r/r P/–). (d) Single comb (r/r p/p).
Fig. 12.6 Complete dominance in chickens

R/r P/p × R/r P/p

<table>
<thead>
<tr>
<th>a) P generation</th>
<th>Parent 1 ♀</th>
<th>Parent 2 ♂</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parental phenotype</td>
<td>Rose comb</td>
<td>Pea comb</td>
</tr>
<tr>
<td>Diploid parental genotype</td>
<td>R/R p/p</td>
<td>r/r P/P</td>
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<tr>
<td>Haploid gametes</td>
<td>R p</td>
<td>r P</td>
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<tr>
<th>Parent 2 ♂ gametes</th>
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<tbody>
<tr>
<td>F1 generation CB</td>
</tr>
<tr>
<td>3/4 P/−</td>
</tr>
<tr>
<td>1/4 p/p</td>
</tr>
<tr>
<td>1/4 r/r</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Parent 1 ♀ gametes</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1 genotypes: All R/r P/p</td>
</tr>
<tr>
<td>F1 phenotypes: All walnut comb</td>
</tr>
</tbody>
</table>

Combined F2 ratios: | Expected F2 phenotypic proportions |
b. Fruit shape in summer squash shows a **9:6:1** ratio. Two genes are involved, each **completely dominant**. Interaction between the two loci produces a new phenotype.

i. Long fruit (a/a b/b) are always true-breeding.

ii. Sphere-shaped fruit (A/– b/b or a/a B/–) are not always true-breeding, and sometimes produce long (a/a b/b) or disk-shaped (A/– B/–) fruit.

iii. A cross between true-breeding spherical strains (A/A b/b X a/a B/B) produces a disk-shaped F₁. The F₂ will be **9/16** disk-shaped (A/– B/–), **6/16** spherical (A/– b/b or a/a B/–) and **1/16** long (a/a b/b). This modification of the Mendelian ratio indicates that two loci are involved.

iv. The precise molecular basis of these phenotypes is unknown.
Fig. 12.7 Generation of an F₂ 9:6:1 ratio for fruit shape in summer squash

P: A/a b/l
   sphere-shaped

×

F₁: A/a B/l
    disk-shaped

F₁ × F₁:

F₂ ratio for A/a × A/a

3/16 A/A b/l sphere-shaped
1/16 A/a B/l disk-shaped
1/16 a/a b/l long-shaped

F₂ ratio for B/l × B/l

3/16 A/A b/l sphere-shaped
3/16 A/a b/l sphere-shaped
1/16 a/a b/l long-shaped

Combined F₂ ratios

F₂ phenotypic proportions

3/16 disk-shaped
5/16 sphere-shaped
1/16 long-shaped
Epistasis

1. In epistasis, one gene masks the expression of another, but no new phenotype is produced.
   a. A gene that masks another is epistatic.
   b. A gene that gets masked is hypostatic.

2. Several possibilities for interaction exist, all producing modifications in the 9:3:3:1 dihybrid ratio:
   a. Epistasis may be caused by recessive alleles, so that a/a masks the effect of B (recessive epistasis).
   b. Epistasis may be caused by a dominant allele, so that A masks the effect of B.
   c. Epistasis may occur in both directions between genes, requiring both A and B to produce a particular phenotype (duplicate recessive epistasis).
3. Recessive epistasis occurs in coat color determination in rodents, which show a 9:3:4 ratio.

a. Wild mice have individual hairs with an agouti pattern, bands of black (or brown) and yellow pigment. Agouti hairs are produced by a dominant allele, A. Mice with genotype a/a do not produce the yellow bands, and have solid-colored hairs.

b. The B allele produces black pigment, while b/b mice produce brown pigment. The A allele is epistatic over B and b, in that it will insert bands of yellow color between either black or brown.

c. The C allele is responsible for development of any color at all, and so it is epistatic over both the agouti (A) and the pigment (B) gene loci. A mouse with genotype c/c will be albino, regardless of its genotype at the A and B loci.

d. In the cross A/a C/c X A/a C/c, the offspring will be:
   i. 9/16 agouti (A/− C/−).
   ii. 3/16 solid (a/a C/−).
   iii. 4/16 albino (3/16 A/− c/c + 1/16 a/a c/c).
Fig. 12.9 Recessive epistasis: Generation of an $F_2$ 9:3:4 ratio for coat color in rodents
4. **Duplicate recessive epistasis** (complementary gene action) is seen in flower color determination in sweet peas, which shows a 9:7 ratio.
   a. Purple is dominant for flower color, and when a true-breeding purple plant is crossed with a true-breeding white one, the F$_2$ shows a typical 3:1 ratio.
   b. White strains usually breed true, but occasionally the cross of two different white strains (p/p C/C X P/P c/c) will produce an F$_1$ that is entirely purple (P/p C/c).
      i. The F$_2$ of this cross will be 9/16 purple (P/– C/–), and 7/16 white (3/16 P/– c/c + 3/16 p/p C/– + 1/16 p/p c/c).
      ii. All of the white F$_2$ plants will breed true, as will 1/9 of the purple F$_2$ plants (P/P C/C).
   c. Two genes appear to be involved. The C/c alleles determine whether the flower can have color, and the P/p alleles determine whether purple is produced.

5. Interactions between genes can produce many types of phenotypes. They are detected by deviations from expected phenotypic ratios.

6. The complex relationships of epistasis play a role in many human genetic disorders, further complicating their analysis.
Fig. 12.10  Duplicate recessive epistasis: Generation of an $F_2$ 9:7 ratio for flower color in sweet peas

P  
\[ \text{C/C p/p white} \times \text{c/c p/P white} \]

\[ \text{F}_1 \]
\[ \text{C/c P/p purple} \]

\[ \text{F}_1 \times \text{F}_1 \]
\[ \text{C/c P/p purple} \times \text{C/c P/p purple} \]

<table>
<thead>
<tr>
<th>$F_2$ ratio for C/c x C/c</th>
<th>$F_2$ ratio for P/p x P/p</th>
<th>Combined $F_2$ ratios</th>
<th>$F_2$ phenotypic proportions</th>
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</thead>
<tbody>
<tr>
<td>3/16 purple</td>
<td>9/16 Cl/- P/-</td>
<td>9/16 purple</td>
<td></td>
</tr>
<tr>
<td>3/16 white</td>
<td>1/16 c/c P/-</td>
<td>3/16 white</td>
<td></td>
</tr>
<tr>
<td>3/16 white</td>
<td>1/16 c/c P/-</td>
<td>7/16 white</td>
<td></td>
</tr>
<tr>
<td>More than four phenotypic classes</td>
<td>A/A B/B</td>
<td>A/A B/b</td>
<td>A/a B/B</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>A and B both incompletely dominant</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>A incompletely and B completely dominant</td>
<td>3</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Four phenotypic classes</td>
<td>A and B both completely dominant (classic ratio)</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>a/a epistatic to B and b; recessive epistasis</td>
<td>9</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>A epistatic to B and b; dominant epistasis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A epistatic to B and b; b/b epistatic to A and a; dominant and recessive epistasis</td>
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<tr>
<td>Fewer than four phenotypic classes</td>
<td>a/a epistatic to B and b; b/b epistatic to A and a; duplicate recessive epistasis</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>A epistatic to B and b; B epistatic to A and a; duplicate dominant epistasis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duplicate interaction</td>
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*The 13 is composed of the 12 classes immediately above plus the one a/a b/b from the last column.

Essential Genes and Lethal Alleles

1. Some genes are required for life (essential genes), and mutations in them (lethal alleles) may result in death. Dominant lethal alleles result in death of both homozygotes and heterozygotes, while recessive lethal alleles cause death only when homozygous.

2. An example is the yellow body color gene in mice (Cuenot, 1905):
   a. Yellow crossed with nonyellow results in a ratio of 1 yellow : 1 nonyellow. This suggests yellow is heterozygous.
   b. Yellow mice never breed true, another indication of heterozygosity. When yellow is bred with yellow, the result is about 2 yellow : 1 nonyellow (instead of the predicted 3:1).
   c. Castle and Little (1910) proposed that yellow homozygotes die in utero, and are therefore missing from the progeny. The yellow allele has a dominant effect on coat color, but also acts as a recessive lethal allele.
   d. Yellow is an allele of the agouti locus, designated A^Y. Figure shows the yellow x yellow cross.
      i. The cross is A^Y/A^1 X A^Y/A^1, and death of the homozygous yellow animals (A^Y/A^Y) results in a 2:1 ratio.
Essential Genes and Lethal Alleles

ii. When two heterozygotes are crossed and produce a 2:1 ratio of progeny, a recessive lethal allele is suspected.

e. Molecular cloning of the agouti locus assists in analysis of these phenotypes:

i. Wild-type agouti mice (A+/A+) express the agouti gene only during hair development in the days after birth, and when plucked hair is being regenerated. Gene expression is seen in no other tissues and at no other time.

ii. Heterozygous mice (A^Y/A+) express the A^Y allele at high levels in all tissues during all developmental stages. Tissue-specific regulation appears to be lost in the A^Y allele.
Essential Genes and Lethal Alleles

iii. The \( A^Y \) allele transcript RNA is 50% longer than that of the wild-type allele (\( A^+ \)). This is because:

1. The \( A^Y \) allele results from deletion of an upstream sequence, removing the normal promoter of the agouti gene.
2. The gene is transcribed from the promoter of an upstream gene called Raly. The beginning of the sequence encoding Raly is fused with the agouti gene, producing a longer transcript.

iv. Embryonic lethality of \( A^Y/ A^Y \) mice probably results from lack of Eif2s2 gene activity (the gene that is located between Raly and Agouti locus in mice) rather than from the defective agouti gene.
The yellow allele has a **dominant** effect on coat color, but also acts as a **recessive lethal** allele.
Human examples of recessive lethal alleles

A. **Tay-Sachs disease**, resulting from an inactive gene for the enzyme hexosaminidase. Homozygous individuals develop neurological symptoms before 1 year of age, and usually die within the first 3-4 years of life.

B. **Hemophilia** results from an X-linked recessive allele, and is lethal if untreated.

A dominant lethal gene causes **Huntington disease**, characterized by progressing central nervous system degeneration. The phenotype is not expressed until individuals are in their 30s. Dominant lethals are rare, since death before reproduction would eliminate the gene from the pool.
Gene Expression and the Environment

1. Development of a multicellular organism from a zygote is a series of generally irreversible phenotypic changes resulting from interaction of the genome and the environment. Four major processes are involved:
   a. Replication of genetic material.
   b. Growth.
   c. Differentiation of cells into types.
   d. Arrangement of cell types into defined tissues and organs.

2. Internal and external environments interact with the genes by controlling their expression and interacting with their products.
Penetrance and Expressivity

1. Penetrance describes how completely the presence of an allele corresponds with the presence of a trait. It depends on both the genotype (e.g., epistatic genes) and the environment of the individual.
   a. If all those carrying a dominant mutant allele develop the mutant phenotype, the allele is completely (100%) penetrant.
   b. If some individuals with the allele do not show the phenotype, penetrance is incomplete. If 80% of individuals with the gene show the trait, the gene has 80% penetrance.
   c. Human examples include:
      i. *Brachydactyly* involves abnormalities of the fingers, and shows 50–80% penetrance.
      ii. Many cancer genes are thought to have low penetrance, making them harder to identify and characterize.
Penetrance and Expressivity

2. Expressivity describes variation in expression of a gene or genotype in individuals.
   
a. Two individuals with the same mutation may develop different phenotypes, due to variable expressivity of that allele.

b. Like penetrance, expressivity depends on both genotype and environment, and may be constant or variable.

c. A human example is osteogenesis imperfecta, inherited as an autosomal dominant with nearly 100% penetrance.
   
i. Three traits are associated with the allele:
      
      (1) Blueness of the sclerae (whites of eyes).
      (2) Very fragile bones.
      (3) Deafness.

   ii. Osteogenesis imperfecta shows variable expressivity, because an individual with the allele may have 1, 2 or all 3 of the above symptoms, in any combination. Bone fragility is also highly variable.
Fig. 12.12 Illustrations of the concepts of penetrance and expressivity in the phenotypic expression of a genotype

(a) Complete penetrance
Identical known genotypes yield 100% expected phenotype

(b) Constant expressivity
Identical known genotypes with no expressivity effect yield 100% expected phenotype

(c) Incomplete penetrance with variable expressivity
Identical known genotypes produce a broad range of phenotypes due to varying degrees of gene activation and expression
Genes have both incomplete penetrance and variable expressivity: **neurofibromatosis**

a. The allele is an autosomal dominant that shows **50–80% penetrance** and **variable expressivity**.

b. Individuals with the allele show a wide range of phenotypes:
   
i. The mildest form of the disease is a few pigmented areas on the skin (café-au-lait spots).
   
ii. More severe cases may include:
       (1) Neurofibroma tumors of various sizes.
       (2) High blood pressure.
       (3) Speech impediments.
       (4) Headaches.
       (5) Large head.
       (6) Short stature.
       (7) Tumors of eye, brain or spinal cord.
       (8) Curvature of the spine.
Effects of the Environment

• Age of onset

• Sex of the individual
  • Sex-limited traits
  • Sex-influenced traits

• Temperature

• Chemicals
  • phenocopy
Effects of the Environment

1. **Age of onset** is an effect of the individual’s *internal environment*. Different genes are expressed at different times during the life cycle, and programmed activation and inactivation of genes influences many traits. Human examples include:
   a. **Pattern baldness**, appearing in males aged 20–30 years.
   b. **Duchenne muscular dystrophy**, appearing in children aged 2–5 years.

2. **Sex of the individual** affects the expression of some autosomal genes.
   a. **Sex-limited traits** appear in one sex but not the other. Examples include:
      i. **Milk production** in dairy cattle, where both sexes have milk genes, but only females express them.
      ii. **Horn formation** in some sheep species, where only males express the genes used to produce horns.
      iii. **Facial hair** distribution in humans.
b. **Sex-influenced traits** appear in both sexes, but the sexes show either a difference in frequency of occurrence or an altered relationship between genotype and phenotype. Human examples include:

i. Pattern baldness, controlled by an *autosomal gene* that is dominant in males and recessive in females.
   (1) The genotype b/b produces pattern baldness in both men and women.
   (2) The genotype b+/b+ gives a nonbald phenotype in both sexes.
   (3) The genotype b+/b will lead to the bald phenotype in men, and the nonbald phenotype in women.

ii. Cleft lip and palate (2:1 ratio of males to females).

iii. Clubfoot (2:1).

iv. Gout (8:1).

v. Rheumatoid arthritis (1:3).

vi. Osteoporosis (1:3).

vii. Systematic lupus erythematosus (1:9).
Fig. 12.14a  Sex-influenced inheritance of pattern baldness in humans

Parental phenotype

Parental genotype

Haploid gametes

Progeny

Progeny genotypes: All $b^+ / b$

Progeny phenotypes: Nonbald ♀; bald ♂ because the trait is sex-influenced

Fig. 12.14b  Sex-influenced inheritance of pattern baldness in humans

<table>
<thead>
<tr>
<th>Phenotypes</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonbald</td>
<td>$b^+/b^+$</td>
<td>$b^+/b^+$</td>
</tr>
<tr>
<td>Bald</td>
<td>$b^-/b^+$</td>
<td>$b^-/b^+$</td>
</tr>
</tbody>
</table>

F2 genotypes:
- $\frac{1}{4} b^+/b^+$
- $\frac{1}{4} b^-/b^+$
- $\frac{1}{4} b^-/b^-$
- $\frac{1}{4} b/b$

F2 phenotypes:
- $\frac{1}{4}$ nonbald whether male or female
- $\frac{1}{4}$ nonbald if female, bald if male
- $\frac{1}{4}$ bald whether female or male
3. Temperature may alter the activity of enzymes so that they function normally at one temperature but are nonfunctional at another. An example is fur color in Himalayan rabbits.

   a. These white rabbits develop darker fur on the cooler parts of their bodies (ears, nose and paws).
   b. Since all body cells have the same genotype, this fur pattern might result from environmental influences. This was tested by raising Himalayan rabbits under different temperature conditions:
      i. Rabbits raised above 30°C were entirely white.
      ii. Rabbits raised at 25°C had the typical Himalayan phenotype.
      iii. Rabbits raised at 25°C with part of the body experimentally cooled to below 25°C, had a dark spot on the experimentally cooled part.
• **Chemicals** can have significant effects. Two examples:

  a. **Phenylketonuria (PKU)** is an autosomal recessive defect in metabolism of the amino acid phenylalanine. If not treated by restricting **phenylalanine** in the diet, severe mental retardation and other symptoms result.

  b. A **phenocopy** is a modification of the phenotype caused by environmental conditions, **mimicking a known gene mutation**. Phenocopies are not hereditary, and the individual does not carry the allele(s) being mimicked. Examples of phenocopies include:

    i. Rubella, which produces cataracts, deafness and heart defects in a fetus whose mother is infected during the first 12 weeks of pregnancy, mimics rare recessive alleles.

    ii. The drug thalidomide, taken on days 35–50 of gestation, mimics the effects of the genetic disorder phocomelia, suppressing development of long bones in the limbs.
Nature versus Nurture

1. Phenotypes seen for many traits are influenced by both genes and environment. Some human examples:

   a. Human height has both genetic and environmental components.

      i. Genetically, children tend to have about the same stature as their parents, and several genetic forms of dwarfism are known (achondroplasia is an example).

      ii. Environmentally, diet and health care are probably responsible for the increase in human height of about 1 inch per generation over the last century.

   b. Alcoholism is an example of a behavioral trait influenced by both genes and environment.

      i. A genetic influence is shown in studies of adopted children. Those with alcoholic biological fathers are significantly more likely to become alcoholics than those with non-alcoholic biological fathers.
ii. Environment plays a key role also, since alcoholism can only develop if alcohol is available.

iii. Genes make individuals more or less susceptible to alcohol abuse, perhaps by affecting metabolism of alcohol or development of personality traits involved in drinking, but the genes alone do not produce the phenotype.

c. **Human intelligence** is an example of a very complex relationship between genes and environment.

i. Genetic disorders are known to produce mental retardation. Examples are PKU and Down syndrome. Genes also influence IQ among non-retarded people, with adopted children scoring closer to their biological parents than to their adoptive parents.

ii. Environmental influences are seen in studies of **identical twins**, who frequently differ in IQ scores.

iii. **Interactions between many genes and all aspects of the environment** are involved in forming human intelligence. Genes can’t be changed, but the environment can be altered to affect this very complex phenotype.
C. Complications: Pleiotropy

- One gene affects many characters
- Sickling allele of hemoglobin