Chapter 14: Patterns of Inheritance

- INTRODUCTION TO GENETICS
- APPLIED GENETICS
Chapter 14A: INTRODUCTION TO GENETICS

- Mendel
- Rules and Terminology for Examination of Genetic Inheritance
- Expanding the Rules and Terminology to follow two (or more) genes in a cross
- Beyond simple genetics: Mendel picked easy fights
- Sex determination and sex chromosomes
• Compare and describe the relationship between:

  – P generation (or P1) / F1 generation / F2 generation
  – phenotype / genotype
  – gene / locus / alleles
  – dominant allele or trait / recessive allele or trait
  – homozygous / heterozygous / hybrid
The foundation of genetics: Mendel’s laws of inheritance

- The basic rules of inheritance were first demonstrated by Gregor Mendel in the mid-1800s.

- At the time of Mendel’s work, most thought that parental traits were fluids that “blend” in offspring.

- Mendel recognized that this model did not explain what he observed.
The foundation of genetics: Mendel’s laws of inheritance

- Mendel chose a model system and carefully established testing conditions
  - he used pea plants that he could outcross or allow to self-fertilize
  - he chose traits that had two clear possible outcomes (yellow or green seeds, etc.)
  - he established true-breeding or “pure” lines to use for genetic crosses
terminology for genetic crosses

- **P generation** (or **P₁**) = parental generation
- **F₁ generation** = first generation offspring (from *filial*)
- **F₂ generation** = second generation offspring
- **phenotype** – appearance or characteristic of an organism
- **genotype** – genetic makeup of an organism, determines phenotype
- **gene** – unit of heredity; controls a trait that determines a phenotype
- **locus** – the location of a particular gene on a chromosome
- **alleles** – alternative versions of a gene
- **dominant** – allele that dominates over others in determining phenotype
- **recessive** – allele whose phenotypic expression is “hidden” when a dominant allele is present
- **hybrid** – offspring from a cross between two “pure” lines of different, competing phenotypes
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Mendel’s Law of Segregation

- When Mendel crossed pure lines of different, competing phenotypes.

- F₁ generation was uniform and matched one of the parents’ phenotypes.

- Example: P₁ yellow seed X green seed → all F₁ yellow seed.
Mendel’s Law of Segregation

- when F₁ plants were crossed or selfed, the F₂ plants had both P₁ phenotypes in a ratio of roughly 3:1

- using offspring from above
  \[ F₁ \times F₁ \rightarrow F₂ \]
  3 yellow seed: 1 green seed

- So…recessive traits are not lost in a mixing of parental phenotypes – they are merely hidden in some “carrier” individuals
<table>
<thead>
<tr>
<th>Character</th>
<th>Dominant Trait</th>
<th>×</th>
<th>Recessive Trait</th>
<th>F₂ Generation Dominant:Recessive</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flower color</td>
<td>Purple</td>
<td>×</td>
<td>White</td>
<td>705:224</td>
<td>3.15:1</td>
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<tr>
<td>Flower position</td>
<td>Axial</td>
<td>×</td>
<td>Terminal</td>
<td>651:207</td>
<td>3.14:1</td>
</tr>
<tr>
<td>Seed color</td>
<td>Yellow</td>
<td>×</td>
<td>Green</td>
<td>6022:2001</td>
<td>3.01:1</td>
</tr>
<tr>
<td>Seed shape</td>
<td>Round</td>
<td>×</td>
<td>Wrinkled</td>
<td>5474:1850</td>
<td>2.96:1</td>
</tr>
<tr>
<td>Pod shape</td>
<td>Inflated</td>
<td>×</td>
<td>Constricted</td>
<td>882:299</td>
<td>2.95:1</td>
</tr>
<tr>
<td>Pod color</td>
<td>Green</td>
<td>×</td>
<td>Yellow</td>
<td>428:152</td>
<td>2.82:1</td>
</tr>
<tr>
<td>Stem length</td>
<td>Tall</td>
<td>×</td>
<td>Dwarf</td>
<td>787:277</td>
<td>2.84:1</td>
</tr>
</tbody>
</table>
Mendel’s Law of Segregation

- Mendel explained these ratios with what we now call his **law of segregation**; stated in modern terms:
  - individuals normally carry two alleles for each gene; these alleles must segregate in production of sex cells
  - later investigations of cell division revealed the mechanism for segregation: the pairing and subsequent separation of homologous chromosomes during meiosis
Genotype vs. Phenotype

- phenotype is the actual appearance or characteristic, and is determined by genotype
  - knowing the phenotype will not always directly reveal the genotype (recessive traits can be masked)
- genotype is the listing of the actual alleles present; if you know the genotype, you should be able to predict the phenotype
Genotype vs. Phenotype

- genotypes are either homozygous or heterozygous
  - homozygous – the homologous chromosomes have the same allele at the locus in question; the trait from that allele will be expressed
  - heterozygous – the homologous chromosomes have different alleles at the locus; if there is a dominant allele the trait of the dominant allele will be expressed
- the same letter is used to indicate all alleles (superscripts or subscripts are sometimes needed, if there are more than 2 alleles known)
- DOMINANT ALLELES ARE CAPITALIZED; recessive alleles are lowercase
Compare and describe the relationship between:

- P generation (or P1) / F1 generation / F2 generation
- phenotype / genotype
- gene / locus / alleles
- dominant allele or trait / recessive allele or trait
- homozygous / heterozygous / hybrid
• Draw a Punnett square and list the predicted fractions for each genotype and phenotype for this cross:

heterozygous (yellow seeds) X heterozygous (yellow seeds)

...where yellow seeds is dominant over green seeds
Applying the Law of Segregation: Probability

- **rules of probability** govern genetic inheritance

- the likelihood of a sex cell carrying a particular allele is determined by probability, its expected frequency of occurrence

- expressed in fractions, decimal fractions, percentages, or ratios – any of these is fine to use

- the combination of sex cells to form a zygote is generally ruled by probability as well

- thus, the rules of probability govern genetics
Applying the Law of Segregation: Probability

- **product rule** – when independent but *not mutually exclusive* events are combined, you *multiply their individual probabilities* to get the overall probability of the result.

- **sum rule** – if there is more than one way to obtain a result (*mutually exclusive events*), you *add their individual probabilities* to get the overall probability of the result.

- the sum of all possibilities is one (no more, no less)
Applying the Law of Segregation: Probability

- **Punnett square** – way of diagramming genetic crosses that uses the laws of probability
Applying the Law of Segregation: Probability

- **Punnett square** – way of diagramming genetic crosses that uses the laws of probability
• Draw a Punnett square and list the predicted fractions for each genotype and phenotype for this cross:

heterozygous (yellow seeds) X heterozygous (yellow seeds)

...where yellow seeds is dominant over green seeds
practice applying the law of segregation: following one gene in a cross
Applying the Law of Segregation

- more terminology

- **test cross** – mating an individual that has the dominant phenotype for a trait with an individual with the recessive phenotype

- this often will reveal the genotype of the dominant parent, or at least give some idea of the probable genotype
Applying the Law of Segregation

- more terminology

- **monohybrid cross** – cross between individuals that are both heterozygous for the gene that you are following
Applying the Law of Segregation

A monohybrid cross results in a

3:1 phenotype ratio

and

1:2:1 genotype ratio
practice applying the law of segregation: following one gene in a cross

• A pea plant with yellow seeds is crossed with a pea plant with green seeds (P₁ generation). All 131 offspring (F₁ generation) have yellow seeds. What are the likely genotypes of the P₁ plants?
practice applying the law of segregation: following one gene in a cross

- Two of the F₁ plants from before are crossed. What are the expected ratios of phenotypes and genotypes in the F₂ generation?
Study Tip

- be sure to work some examples on your own; the textbook and website have plenty of genetics problems – note how they are typically presented as word problems and expect that format on your test
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[make up about 3 practice two-gene crosses]
Mendel’s Law of Independent Assortment

- **dihybrid cross** – cross between individuals that are both heterozygous for two different genes that you are following

- when Mendel performed dihybrid crosses he found phenotype ratios of 9:3:3:1

- note that this follows the product rule:

  \[3:1 \times 3:1 = 9:3:3:1\]
Mendel’s Law of Independent Assortment

- this led to his **law of independent assortment**:
  - segregation of any one pair of alleles is independent of the segregation of other pairs of alleles
  - we now know that this is also a consequence of events in meiosis
Mendel’s Law of Independent Assortment

- this is also a consequence of events in meiosis – the independent assortment of homologous chromosomes during Meiosis I
P Generation

Fertilization

Gametes

Meiosis

Yellow-round seeds (YYRR) × Green-wrinkled seeds (yyrr)

F1 Generation

Meiosis

All F1 plants produce yellow-round seeds (YyRr)

LAW OF SEGREGATION

Two equally probable arrangements of chromosomes at metaphase I

LAW OF INDEPENDENT ASSORTMENT

1

2

3

F1 Generation

Anaphase I

Metaphase II

Gametes

1/2 YR

1/2 yr

1/2 Yr

1/2 yR

F2 Generation

Fertilization among the F1 plants

9 : 3 Y R : 3 Y r : 1 y R
Mendel’s Law of Independent Assortment

- law of independent assortment doesn’t hold perfectly true for all genes (more on genetic linkage that violates this law later)
Mendel’s Law of Independent Assortment

- using the law of independent assortment in genetic problems

- with independent assortment a dihybrid cross is simply two separate monohybrid crosses multiplied

- avoid making tedious and difficult Punnett squares like

- we will work examples in class; be sure to try some on your own

The hard way…

No no no!!!
Mendel’s Law of Independent Assortment

An easier way to do $RrGg \times RrGg$

(note for alleles: $R =$ round, $r =$ wrinkled; $G =$ yellow, $g =$ green)

$3$ round
$1$ wrinkled
$X$

$3$ round
$1$ green

$= 9$ round, yellow
$3$ round, green
$3$ wrinkled, yellow
$1$ wrinkled, green
[make up about 3 practice two-gene crosses]
Mendel’s Law of Independent Assortment

- independent segregation of chromosomes during meiosis I leads to independent assortment
- independent assortment can lead to recombination...
Determine predicted results for the test cross used in the genetic linkage example.
Mendel’s Law of Independent Assortment

- **recombination** – any process that leads to combinations of genotypes not seen in the parents

- **recombinant gametes** – gametes that display a recombinant genotype

- **recombinant offspring** – offspring whose phenotype reveals that they inherited genes from a recombinant gamete
Genetic linkage – independent assortment does not always occur

- genes that are on the same chromosome may not sort independently; such genes are said to be **linked**
Genetic linkage – independent assortment does not always occur

- **crossing over** breaks linkages between genes

- recall crossing over during prophase I between homologous chromosomes; it is the only way to get genetic recombination between genes that are on the same chromosome

- the further apart two genes are, the more likely they are to have crossing over occur between them (thus leading to genetic recombination)
Testcross parents

Gray body, normal wings (F₁ dihybrid)

Replication of chromosomes

Meiosis I: Crossing over between b and vg loci produces new allele combinations.

Meiosis II: Separation of chromatids produces recombinant gametes with the new allele combinations.

Gametes

Recombinant chromosomes

Sperm

Testcross offspring

965 Wild type (gray-normal)
944 Black-vestigial
206 Gray-vestigial
185 Black-normal

Recombination frequency = \( \frac{391 \text{ recombinants}}{2,300 \text{ total offspring}} \times 100 = 17\% \)
• Determine predicted results for the test cross used in the genetic linkage example.
Genetic Maps of Chromosomes

- The percentage of crossing over or recombination is calculated from:

\[
\frac{100 \times \text{number of recombinant offspring}}{\text{the total number of offspring}}
\]

- **map unit** – by convention, one map unit = 1% recombination

- The term cM or centiMorgan is sometimes used for map units, in honor of Thomas Hunt Morgan, the pioneer in gene mapping

- **map distances** between genes on the same chromosome are measured in map units
**Genetic Maps of Chromosomes**

- **linkage group** = all genes on a particular chromosome; tend to be inherited together
Genetic Maps of Chromosomes

- Placement of a gene into a position in a linkage group is genetic mapping.
Discuss how you could map gene C.
Genetic Maps of Chromosomes

- Map distances get less meaningful as they get large
- As genes get further apart, the odds of multiple crossing over events between them increase
- When distances approach 50 map units, the genes appear essentially unlinked
- Many chromosomes have an overall map length of well over 50 map units
- Genetic maps are useful in locating the actual physical location of genes
Genetic Maps of Chromosomes

Garden Pea Genes

<table>
<thead>
<tr>
<th>Chromosome number</th>
<th>Location of genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Flower color</td>
</tr>
<tr>
<td>2</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Flower position</td>
</tr>
<tr>
<td>5</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>
Methods of studying human inheritance: family pedigree analysis

- **pedigree** – a chart summarizing phenotypes and/or genotypes within a family over several generations

- Pedigree analyses only work well when a single locus is involved in determining a phenotype (so-called Mendelian traits)
Methods of studying human inheritance: family pedigree analysis

- **pedigree** – a chart summarizing phenotypes and/or genotypes within a family over several generations

- Pedigree analyses only work well when a single locus is involved in determining a phenotype (so-called Mendelian traits)
A Pedigree Analysis of Albinism

- Successive generations marked by Roman numerals
- Individuals in each generation are marked by Arabic numerals
- Is albinism dominant?
- Is it sex-linked?
Pedigree Analysis

- Is the filled-in trait dominant or recessive?
- Is it sex-linked or not?
Pedigree Analysis

- Is the filled-in trait dominant or recessive?
- Is it sex-linked or not?
Pedigree Analysis

- Is the filled-in trait dominant or recessive?
- Is it sex-linked or not?
• Describe three different ways in which sex is determined.

• Describe the homogametic and heterogametic sexes for humans and then for birds.
Sex Determination and Sex Chromosomes

- see Ch. 15.2 for textbook coverage of this issue
- sex determination varies between species
  - hermaphroditic organisms – have both sexes in the same individual
  - many animals have sex determined in response to environmental signals
  - most animals have sex determined by genetic inheritance; sex chromosomes are involved
Sex Determination and Sex Chromosomes

- **sex chromosomes**
  - **homogametic sex** – has a pair of similar sex chromosomes; all gametes that individual produces get that kind of sex chromosome
  - **heterogametic sex** – has two different sex chromosomes, and makes gametes with two different types of sex chromosome
  - the sex chromosome inherited from the heterogametic sex generally determines the sex of the offspring
- all the other, non-sex chromosomes are called **autosomes**
Sex Determination and Sex Chromosomes

- usually, the sex chromosome found in the homogametic sex is considerably larger, and the shorter sex chromosome found only in the heterogametic sex has few genes

- in humans, females are XX and males are XY (not all do it this way – birds are essentially reversed in this)

- X and Y chromosomes have regions of homology (sequence similarity) that allow for pairing during meiosis I
• Describe three different ways in which sex is determined.

• Describe the homogametic and heterogametic sexes for humans and then for birds.
Sex Determination and Sex Chromosomes

- usually, but not always, the sex determining gene is on the Y chromosome
  - XXY humans are male (Klinefelter syndrome)
  - X_ humans are female (Turner syndrome)
[make up 2-3 sex linkage genetics problems]
sex-linked traits

- genes on sex chromosomes show inheritance patterns that do not fit traditional Mendelian ratios that describe what happens to genes on autosomes.

- in humans (and other species with XY sex determination), a gene found only on the X chromosome is said to be X-linked (which is a type of sex-linked).

  - males only get one X chromosome, from the mother, and are **hemizygous** at every locus found only on the X chromosome.

  - thus, recessive X-linked alleles are expressed more often in males than in females.
sex-linked traits

- X-linked alleles are written with superscripts
sex-linked traits

- human examples of X-linked recessive traits:
  - red-green colorblindness
  - hemophilia

HERE:

carrier female X normal male

carrier = normal phenotype, heterozygous genotype
sex-linked traits

- human examples of X-linked recessive traits:
  - red-green colorblindness
  - hemophilia

HERE:

homozygous normal female X male with the trait
sex-linked traits

- human examples of X-linked recessive traits:
  - red-green colorblindness
  - hemophilia

HERE:

carrier female X male with the trait
[make up 2-3 sex linkage genetics problems]
Human X Chromosome Gene Map (1)

- Ichthyosis, X-linked
- Placental steroid sulfatase deficiency
- Kallmann syndrome
- Chondrodysplasia punctata, X-linked recessive
- Adrenal hypoplasia
- Glycerol kinase deficiency
- Androgen insensitivity
- PRPS-related gout
- Lowe syndrome
- Hemophilia A
- G6PD deficiency: favism
- Drug-sensitive anemia
- Chronic hemolytic anemia
- Manic-depressive illness, X-linked
- Colorblindness, (several forms)
- Dyskeratosis congenita
- TKCR syndrome
- Adrenoleukodystrophy
- Adrenomyeloneuropathy
- Emery-Dreifuss muscular dystrophy
- Diabetes insipidus, renal
- Myotubular myopathy, X-linked
- Norrie disease
- Retinitis pigmentosa-2
- Sideroblastic anemia
- Aarskog-Scott syndrome
- PGK deficiency
- Hemolytic anemia
- Anhidrotic ectodermal dysplasia
- Pelizaeus-Merzbacher disease
- Alport syndrome
- Fabry disease
Human X Chromosome Gene Map (2)

- Duchenne muscular dystrophy
- Becker muscular dystrophy
- Chronic granulomatous disease
- Retinitis pigmentosa-3
- Hypophosphatemia
- Aicardi syndrome
- Hypomagnesemia, X-linked
- Ocular albinism
- Retinoschisis
- Ornithine transcarbamylase deficiency
- Incontinentia pigmenti
- Wiskott-Aldrich syndrome
- Menkes syndrome
- Charcot-Marie-Tooth neuropathy
- Choroideremia
- Cleft palate, X-linked
- Spastic paraplegia, X-linked, uncomplicated
- Deafness with stapes fixation
- Lesch-Nyhan syndrome
- HPRT-related gout
- Hunter syndrome
- Hemophilia B
- Agammaglobulinemia
- Kennedy disease
- Immunodeficiency, X-linked, with hyper IgM
- Lymphoproliferative syndrome
- Albinism-deafness syndrome
- Fragile-X syndrome
• Explain dosage compensation in fruit flies and then in mammals; for mammals, use the terms Barr body and mosaicism
Dosage Compensation

- it is not always good to have twice as much of a chromosome, or half as much

- **dosage compensation** – a mechanism for equalizing the overall expression of an X-linked gene in both males and females
  - some organisms (like fruit flies) ramp up X-linked gene expression in the heterogametic sex
  - some (like humans and other mammals) use inactivation of most of one of the X chromosomes

- **Barr body** – condensed, mostly inactivated X chromosome visible during interphase in most mammalian cells
Dosage Compensation

- **variegation** or mosaicism – mixes in phenotypic appearance in an organism due to expression of X-linked genes and variable, random inactivation patterns for X chromosomes

- examples: calico cat, tortoiseshell cat, patchy dry skin in human females
• Explain dosage compensation in fruit flies and then in mammals; for mammals, use the terms Barr body and mosaicism
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- Sex determination and sex chromosomes (Ch. 15.3)
• Give the phenotype ratio results for a cross between:
  – pink and red snapdragons
  – pink and pink snapdragons
  – white and red snapdragons
Beyond simple genetics: Mendel picked easy fights

- Modifications must be made to Mendel’s laws for linked genes.
- There are other situations that do not fit the “simple” cases that Mendel used.
- **Incomplete dominance** – the heterozygote has a phenotype that is intermediate between the two homozygous states.
- Really, the term dominance has no true meaning here.
Beyond simple genetics: Mendel picked easy fights

- **incomplete dominance** – example: red, pink, and white snapdragon flowers
• Give the phenotype ratio results for a cross between:
  
  – pink and red snapdragons
  – pink and pink snapdragons
  – white and red snapdragons
Beyond simple genetics: Mendel picked easy fights

- **codominance** – the heterozygote expresses characteristics of both alleles; very much like incomplete dominance
  - not an intermediate form, instead you see each allele distinctly expressed
  - roan cattle, expressing both red and white hairs, are a good example
  - the difference between incomplete dominance and codominance is essentially a case of splitting hairs
  - one of the best examples is the ABO human blood type, which will be covered later
  - how to spot codominance or incomplete dominance: monohybrid crosses with a 1:2:1 phenotype ratio
[make up 2-3 blood group genetics problems]
Beyond simple genetics: Mendel picked easy fights

- **multiple alleles** – it is very common for there to be more than two allele types for a given locus; any time there are three or more alleles types involved, we say that there are multiple alleles.

- dominance relationships can vary between multiple alleles.

- example: rabbit coat color is influenced by a gene that has four known alleles.
Beyond simple genetics: human ABO blood types

- **multiple alleles** example: human ABO blood types

  - the main blood type is determined by a single locus with three known alleles ($I^A$, $I^B$, $i^O$)

  - $I^A$ and $I^B$ alleles are codominant with respect to each other

  - the $I^A$ allele leads to the expression of type A antigen on the surface of red blood cells

  - the $I^B$ allele leads to the expression of type B antigen on the surface of red blood cells

  - $i^O$ is a recessive allele; the $i^O$ allele does not lead to expression of a cell surface antigen
Beyond simple genetics: human ABO blood types

resulting blood types:

- $I^A I^A$ or $I^A i^O$ genotype produce only the A antigen; blood type A
- $I^B I^B$ or $I^B i^O$ genotype produce only the B antigen; blood type B
- $I^A I^B$ genotype produces both the A antigen and B antigen; blood type AB
- $i^O i^O$ genotype produces no A or B antigens; blood type O

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Phenotype (Blood Group)</th>
<th>Red Blood Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>$I^A I^A$ or $I^A i$</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>$I^B I^B$ or $I^B i$</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>$I^A I^B$</td>
<td>AB</td>
<td></td>
</tr>
<tr>
<td>$ii$</td>
<td>O</td>
<td></td>
</tr>
</tbody>
</table>
[make up 2-3 blood group genetics problems]
Beyond simple genetics: human ABO blood types

- Blood transfusions (or any transplants) must be of the appropriate type, because the blood of individuals contains antibodies against the antigens not contained on its red blood cells.

- Thus, type O can only accept type O blood or organs.

- Type AB can accept any type blood or organs (A, B, AB or O); etc.

- There are other blood type factors, such as Rh factor, that must be taken into account.

- Blood type is used in paternity or maternity cases only as a means to rule out possible parents.
Beyond simple genetics: Pleiotrophy

- **pleiotrophy**: one gene, many phenotypes
  - one gene affects more than one characteristic
  - usually only one gene product is directly involved, and its status affects many things
  - many disease genes are pleiotrophic (examples, cystic fibrosis, sickle cell anemia)
Beyond simple genetics: one phenotype, many genes

- **gene interactions** – two or more genes interact to produce a novel phenotype

- hallmark of gene interactions:
  - exactly 4 phenotypes are found
  - certain crosses will produce a 9:3:3:1 phenotype ratio in offspring (thus indicating that they are dihybrid crosses)
Beyond simple genetics: one phenotype, many genes

- **gene interactions** – two or more genes interact to produce a novel phenotype

- examples: rooster combs; coat color in Labrador retrievers
Beyond simple genetics: one phenotype, many genes

<table>
<thead>
<tr>
<th>Gene Interactions in Labrador Retriever Coat Color</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ee</strong></td>
</tr>
<tr>
<td>No dark pigment in fur</td>
</tr>
<tr>
<td>Yellow Lab</td>
</tr>
<tr>
<td><strong>eebb</strong></td>
</tr>
<tr>
<td>Yellow fur, brown nose, lips, eye rims</td>
</tr>
<tr>
<td><strong>eeB_</strong></td>
</tr>
<tr>
<td>Yellow fur, black nose, lips, eye rims</td>
</tr>
<tr>
<td><strong>E_</strong></td>
</tr>
<tr>
<td>Dark pigment in fur</td>
</tr>
<tr>
<td><strong>E_bb</strong></td>
</tr>
<tr>
<td>Brown fur, nose, lips, eye rims</td>
</tr>
<tr>
<td><strong>E_B_</strong></td>
</tr>
<tr>
<td>Black fur, nose, lips, eye rims</td>
</tr>
</tbody>
</table>

![Images of Labrador Retrievers](image1.png)
Beyond simple genetics: one phenotype, many genes

- **epistasis** – one gene influences the phenotype that a second gene usually controls, masking any effects of alleles at the second gene

- the name literally means “stopping” or “standing upon”

- example: albinism is generally epistatic
Beyond simple genetics: one phenotype, many genes

- example: albinism is generally epistatic
Beyond simple genetics: one phenotype, many genes

- spot epistasis by modification of dihybrid cross results, getting ratios like 9:7 or 9:3:4 instead of 9:3:3:1
Beyond simple genetics: one phenotype, many genes

- **polygenic inheritance** – multiple, independent genes have similar, additive effects on a characteristic

- Examples include height and skin color in humans

- Most economically important traits are polygenic (cow milk production, cattle weight, corn crop yield, etc.)
Beyond simple genetics: one phenotype, many genes

- **polygenic inheritance**

  - polygenic traits don’t fall easily into distinct categories; instead, they usually are measured traits (quantitative traits)
Beyond simple genetics: one phenotype, many genes

- **Polygenic inheritance**
  - when plotted out for a population, polygenic traits produce a normal distribution curve if mating is random with respect to the trait
Beyond simple genetics: one phenotype, many genes

- **polygenic inheritance**

- When plotted out for a population, polygenic traits produce a **normal distribution curve** if mating is random with respect to the trait.
Do all of these exceptions invalidate Mendel’s laws?
Do all of these exceptions invalidate Mendel’s laws?

- **No.** Mendel’s laws explain the basic situation, and all of these exceptions are best understood in light of the mechanisms that Mendel described.

- Scientists generally try to understand simple cases before moving on to the more baffling ones.

- Often (as here) understanding the simpler cases helps form the basis for understanding the more complicated ones.

- However...it is important to know about these “exceptions” and apparent exceptions, because most genetic inheritance has some aspect of one of these “exceptions” in it.
Chapter 14: Patterns of Inheritance

- INTRODUCTION TO GENETICS
- APPLIED GENETICS
Ch. 14B: APPLIED GENETICS

- Using Genetics in Breeding
- Methods of Studying Human Inheritance
- Autosomal Recessive Genetic Disorders
- Autosomal Dominant Genetic Disorders
- Genetic Testing and Screening in Humans
Using Genetics in Breeding

- **inbreeding** – the mating of closely related individuals (includes self-fertilization)

- typically done to enhance a desirable trait (quantitative or qualitative) that an individual has

- also done to produce homozygous lines ("true-breeding")

- often produces genetically inferior individuals due to unmasking of deleterious recessive traits
Using Genetics in Breeding

- **outbreeding** – mating of essentially unrelated individuals (unclear cut-off, beyond second cousins is generally considered enough)

- **hybrid vigor** – progeny produced by outbreeding often show a clear genetic superiority as a group over their parents when the parents are from mostly inbred lines
Using Genetics in Breeding

- the exact cause of hybrid vigor is not clear, and likely has multiple aspects
  - less expression of deleterious recessive traits certainly plays a role
  - **heterozygote advantage** – some positive attribute that is not found in any homozygous case
  - for example, sometimes expression of one of the allelic forms is good to have under one condition and the other is good under a different condition; expressing both allelic forms allows the organism to do well in both conditions, which may both come up during its life
Ch. 14B: APPLIED GENETICS

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Methods of studying human inheritance

- ethical considerations
- family pedigree analysis
- karyotyping
- human genome project
Methods of studying human inheritance: ethical considerations

- Most genetic research involves producing **inbred lines and controlled genetic crosses**
- Since we can’t (or shouldn’t) really do that with humans, we must use other means
- **Isolated populations** with typically **large families** are often used because they provide much **inbreeding and many data points**
Methods of studying human inheritance: karyotyping

- many genetic problems occur on the large-scale, chromosomal level
- studies of karyotypes are often done to test for such problems
- a karyotype display reveals the composition of chromosomes for an individual
  - a cell sample is taken (white blood cells, amniocentesis, chorionic villus sampling, etc.)
  - cells are grown in culture, and eventually treated to make chromosomes easy to photograph
  - the chromosome images are then analyzed and used to create the karyotype display
- chromosomes are identified by size, position of the centromeres, and staining patterns
Preparation of a Karyotype

(a) Culture blood cells (lymphocytes); add colchicine to stop mitosis at metaphase.

(b) Spin down cells in a centrifuge; discard supernatant.

Add hypotonic salt solution and resuspend cells.

(c) Add fixative (preservative) to cell suspension; add one drop to a slide, dry, and stain.
(a) Amniocentesis

A sample of amniotic fluid can be taken starting at the 14th to 16th week of pregnancy.

Fetus

Placenta

Uterus

Cervix

Centrifugation

FluId

Fetal cells

Biochemical tests can be performed immediately on the amniotic fluid or later on the cultured cells.

Fetal cells must be cultured for several weeks to obtain sufficient numbers for karyotyping.

(b) Chorionic villus sampling (CVS)

A sample of chorionic villus tissue can be taken as early as the 8th to 10th week of pregnancy.

Fetus

Placenta

Chorionic villi

Suction tube inserted through cervix

Biochemical tests

Karyotyping

Several weeks

Several hours

Karyotyping and biochemical tests can be performed on the fetal cells immediately, providing results within a day or so.
Fig. 13.35

A Human Karyotype
A Normal *Homo sapiens* Karyotype

- Mitotic (doubled, or bivalent) chromosomes taken from a white blood cell at metaphase, and then stained with Giemsa stain to reveal differences in the DNA/protein associations.

- What was the sex of this individual?
Karyotype Analysis

- Chromosomes are identified:
  - Size
  - Shape
  - Centromere position
  - Banding pattern
  - Satellites (tiny knobs at end of some chromosomes)
Methods of studying human inheritance: human genome project

- sequencing the human genome provides a means to greatly accelerate studies of human genetics
  - the underlying genetic causes for gene-based traits can be studied more easily (including traits that involve multiple genes)
  - sequence variations can be readily analyzed
  - more sophisticated genetic testing can be performed, leading to the potential for genetically tailored medical treatment
Methods of studying human inheritance: human genome project

- A “complete” draft of the human genome sequence (~3 billion basepairs) was made public in April 2003; there are ~25,000 genes in the genome, based on current interpretations of the sequence.

- Links of interest:
  - completion announcement
  - human genome project general information
  - browse your genome
  - National Human Genome Research Institute
  - Genome News Network
<table>
<thead>
<tr>
<th>Organism</th>
<th>Haploid Genome Size (Mb)</th>
<th>Number of Genes</th>
<th>Genes per Mb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemophilus influenzae (bacterium)</td>
<td>1.8</td>
<td>1,700</td>
<td>940</td>
</tr>
<tr>
<td>Escherichia coli (bacterium)</td>
<td>4.6</td>
<td>4,400</td>
<td>950</td>
</tr>
<tr>
<td>Saccharomyces cerevisiae (yeast)</td>
<td>12</td>
<td>5,800</td>
<td>480</td>
</tr>
<tr>
<td>Caenorhabditis elegans (nematode)</td>
<td>97</td>
<td>19,000</td>
<td>200</td>
</tr>
<tr>
<td>Arabidopsis thaliana (plant)</td>
<td>118</td>
<td>25,500</td>
<td>215</td>
</tr>
<tr>
<td>Drosophila melanogaster (fruit fly)</td>
<td>180</td>
<td>13,700</td>
<td>76</td>
</tr>
<tr>
<td>Oryza sativa (rice)</td>
<td>430</td>
<td>60,000</td>
<td>140</td>
</tr>
<tr>
<td>Danio rerio (zebrafish)</td>
<td>1,700</td>
<td>22,000</td>
<td>13</td>
</tr>
<tr>
<td>Mus musculus (house mouse)</td>
<td>2,600</td>
<td>25,000</td>
<td>11</td>
</tr>
<tr>
<td>Homo sapiens (human)</td>
<td>2,900</td>
<td>25,000</td>
<td>10</td>
</tr>
<tr>
<td>Fritillaria assyriaca (plant)</td>
<td>120,000</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

*Strictly defined, “genome” refers to the haploid genome of an organism. Some values given here are likely to be revised as genome analysis continues. Mb = million base pairs. ND = not determined.
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<table>
<thead>
<tr>
<th>Recessive Traits</th>
<th>Phenotypes</th>
<th>Dominant Traits</th>
<th>Phenotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albinism</td>
<td>Lack of melanin pigmentation</td>
<td>Middigital hair</td>
<td>Presence of hair on middle segment of fingers</td>
</tr>
<tr>
<td>Alkaptonuria</td>
<td>Inability to metabolize homogenistic acid</td>
<td>Brachydactyly</td>
<td>Short fingers</td>
</tr>
<tr>
<td>Red-green color blindness</td>
<td>Inability to distinguish red or green wavelengths of light</td>
<td>Huntington’s disease</td>
<td>Degeneration of nervous system, starting in middle age</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>Abnormal gland secretion, leading to liver degeneration and lung failure</td>
<td>Phenylthiocarbamide (PTC) sensitivity</td>
<td>Ability to taste PTC as bitter</td>
</tr>
<tr>
<td>Duchenne muscular dystrophy</td>
<td>Wasting away of muscles during childhood</td>
<td>Camptodactyly</td>
<td>Inability to straighten the little finger</td>
</tr>
<tr>
<td>Hemophilia</td>
<td>Inability to form blood clots</td>
<td>Hypercholesterolemia (the most common human Mendelian disorder—1 in 500)</td>
<td>Elevated levels of blood cholesterol and risk of heart attack</td>
</tr>
<tr>
<td>Sickle cell anemia</td>
<td>Defective hemoglobin that causes red blood cells to curve and stick together</td>
<td>Polydactyly</td>
<td>Extra fingers and toes</td>
</tr>
</tbody>
</table>
Autosomal recessive genetic disorders in humans

- most genetic disorders are inherited as autosomal recessive traits
- the recessive allele is usually a nonfunctional (or poorly functional) copy of a gene whose product is needed in metabolism
- much genetic research with model organisms (mouse, fruit fly, etc.) uses such traits to determine gene identities and functions
Autosomal recessive genetic disorders in humans: examples

- phenylketonuria (PKU)
- sickle cell anemia
- cystic fibrosis
Autosomal recessive genetic disorders in humans: examples

- phenylketonuria (PKU)

  - most common in those of western European descent; occurs in about 1 in 12,000 human births in the U.S.

  - phenylalanine (an amino acid) is not metabolized properly, leading to a buildup of a toxic compounds that can lead to severe mental retardation

  - treated with a diet that dramatically reduces phenylalanine consumption; potential gene therapy target
Autosomal recessive genetic disorders in humans: examples

- **sickle cell anemia**
  - most common in those of African descent; about 1 in 500 African-Americans have it
  - caused by a mutation in hemoglobin that makes it tend to crystallize when oxygen is not bound to it
    - makes red blood cells take on a sickle shape, which can slow or even block blood flow through veins and capillaries
    - can damage tissues due to lack of oxygen and nutrients, and is very painful
    - shortens lifespan of red blood cells, leading to anemia (low red blood cell count)
Normal hemoglobin

Primary structure

Val  His  Leu  Thr  Pro  Glu  Glu

1    2    3    4    5    6    7

Secondary and tertiary structures

β subunit

Quaternary structure

Normal hemoglobin (top view)

α

β

Function

Molecules do not associate with one another; each carries oxygen.

Red blood cell shape

Normal cells are full of individual hemoglobin molecules, each carrying oxygen.

Sickle-cell hemoglobin

Primary structure

Val  His  Leu  Thr  Pro  Glu  Glu

1    2    3    4    5    6    7

Secondary and tertiary structures

Exposed hydrophobic region

β subunit

Quaternary structure

Sickle-cell hemoglobin

α

β

Function

Molecules interact with one another to crystallize into a fiber; capacity to carry oxygen is greatly reduced.

Red blood cell shape

Fibers of abnormal hemoglobin deform cell into sickle shape.
Autosomal recessive genetic disorders in humans: examples

- **sickle cell anemia**
  - treatments have increased life expectancy, including stimulating fetal hemoglobin production and bone marrow transplants; work continues on gene therapy
  - the heterozygous condition actually leads to increased resistance to malaria, and thus is favored when malaria is present – about 1 in 12 African-Americans are heterozygous and thus “carriers” for sickle cell anemia
Correlation Between Sickle Cell Allele and Malaria

Sickle cell allele in Africa
- 1-5%
- 5-10%
- 10-20%

P. falciparum malaria in Africa
- Malaria
Autosomal recessive genetic disorders in humans: examples

- **cystic fibrosis**
  - most common in those of European descent (in this group, about 1 in 3500 births, with about 1 in 28 phenotypically normal, heterozygous carriers for the trait)
  - abnormal body secretions, particularly in the lungs, due to a defect in ion transport
  - life expectancy short (about 38 years); treatments are limited – has been a target for gene therapy trials
  - heterozygous carriers may be less likely to die from diarrhea-inducing diseases (based on mouse model studies involving cholera)
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Symptom</th>
<th>Defect</th>
<th>Dominant/Recessive</th>
<th>Frequency among Human Births</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystic fibrosis</td>
<td>Mucus clogs lungs, liver, and pancreas</td>
<td>Failure of chloride ion transport mechanism</td>
<td>Recessive</td>
<td>1/2500 (Caucasians)</td>
</tr>
<tr>
<td>Sickle cell anemia</td>
<td>Poor blood circulation</td>
<td>Abnormal hemoglobin molecules</td>
<td>Recessive</td>
<td>1/625 (African Americans)</td>
</tr>
<tr>
<td>Tay-Sachs disease</td>
<td>Deterioration of central nervous system in infancy</td>
<td>Defective enzyme (hexosaminidase A)</td>
<td>Recessive</td>
<td>1/3500 (Ashkenazi Jews)</td>
</tr>
<tr>
<td>Phenylketonuria</td>
<td>Brain fails to develop in infancy</td>
<td>Defective enzyme (phenylalanine hydroxylase)</td>
<td>Recessive</td>
<td>1/12,000</td>
</tr>
<tr>
<td>Hemophilia</td>
<td>Blood fails to clot</td>
<td>Defective blood clotting factor VIII</td>
<td>Sex-linked recessive</td>
<td>1/10,000 (Caucasian males)</td>
</tr>
<tr>
<td>Huntington’s disease</td>
<td>Brain tissue gradually deteriorates in middle age</td>
<td>Production of an inhibitor of brain cell metabolism</td>
<td>Dominant</td>
<td>1/24,000</td>
</tr>
<tr>
<td>Muscular dystrophy</td>
<td>Muscles waste away</td>
<td>Degradation of myelin coating of nerves stimulating muscles</td>
<td>Sex-linked recessive</td>
<td>1/3700 (males)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>Excessive cholesterol levels in blood, leading to heart disease</td>
<td>Abnormal form of cholesterol cell surface receptor</td>
<td>Dominant</td>
<td>1/500</td>
</tr>
</tbody>
</table>
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Human autosomal dominant genetic disorders

- severe dominant genetic disorders are not common, because they are usually not passed on to the next generation (affected individuals usually die before they have children)

- those that do exist typically have late onset of disorder symptoms (late enough for those with the disorder to have had children)
Human autosomal dominant genetic disorders

- the best known autosomal dominant disorder is **Huntington disease** (AKA Huntington’s chorea, or HD)

  - occurs in about 1 in 10,000 human live births in the U.S. (no heterozygous carriers – it is a dominant disorder)
  - affects central nervous system, leading to severe mental and physical deterioration
  - onset of symptoms usually in 30s or 40s
Huntington's Disease

Percent of total with Huntington's allele affected by the disease

Age in years

Huntington's disease
Human autosomal dominant genetic disorders

- HD is one of at least 9 known “trinucleotide repeat disorders” in humans
  - HD is caused by a gene with a [CAG] repeat of 36-100x or more (normal allele has 6-35 of these repeats); more repeats usually means earlier onset
  - fragile X syndrome and myotonic dystrophy are two other examples of trinucleotide repeat disorders

- trinucleotide repeat disorders
Human autosomal dominant genetic disorders

- **hypercholesterolemia** is the most common dominant genetic disorder known in humans (estimate: 1 in 500 have it)
  - generally causes high cholesterol levels in blood
  - leads to heart disease, etc.
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Genetic testing and screening

- conclusive tests for many genetic disorders are now available
- especially with the completing of the sequencing of the human genome, more sophisticated “predictive probability” tests are available, such as for alleles that are associated with higher rates of breast cancer
- although testing gives more knowledge, it has limitations
  - there are often at best limited treatments for the disorder
  - in some cases the test only tells you if you are more or less likely to have a problem
  - this leads to many ethical issues and concerns that are still being addressed
- for a view of a dystopian future based on genetic testing, see the movie “GATTACA”
- to see how scientists are trying to address ethical concerns, visit http://www.ornl.gov/sci/techresources/Human_Genome/elsi/elsi.shtml