Extensions of & Deviations from Mendelian Genetic Principles

Lecture 6

Extensions of Mendelian Principles can alter expected Mendelian ratios

- Multiple alleles
- Codominance
- Incomplete dominance
- Polygenics
- Environmental effects

Introduction

- **Mendelian inheritance** describes inheritance patterns that obey two laws
  - **Law of segregation.**
  - **Law of independent assortment.**

- **Simple Mendelian inheritance** involves
  - A single gene with two different alleles.
  - Alleles display a simple dominant/recessive relationship.

Some phenotypic variation poses a challenge to Mendelian analysis

- There are human characteristics that **don't** follow Mendel's rules

Explanations for some traits:

No definitively **dominant** or **recessive** *allele*

- The level of protein expression,
- The sex of the individual,
- More than two alleles exist,
- Multiple genes involved,
- Gene-environment interactions.

- There are many ways in which two ***alleles*** of a single **gene** may govern the outcome of a trait.
- Table describes several different patterns of Mendelian inheritance.

TABLE 4.1

Different Types of Mendelian Inheritance Patterns

Type	Description
Simple Mendelian	**Inheritance:** This term is commonly applied to the inheritance of alleles that obey Mendel's laws and follow a strict dominant/recessive relationship. In chapter 4, we will see that some genes can be found in three or more alleles, making the relationship more complex. **Molecular:** 50% of the protein normally encoded by two copies of the dominant allele is sufficient to produce the dominant trait.
X linked	**Inheritance:** It involves the inheritance of genes that are located on the X chromosome. In mammals and fruit flies, males are hemizygous for X-linked genes while females have two copies. **Molecular:** If a pair of X-linked alleles shows a simple dominant/recessive relationship, 50% of the protein encoded by two copies of the dominant allele is sufficient to produce the dominant trait (in the female).
Lethal alleles	**Inheritance:** An allele that has the potential of causing the death of an organism. **Molecular:** Lethal alleles are most commonly loss-of-function alleles that encode proteins that are necessary for survival. In rare cases, the alleles may be in nonessential genes that change a protein to function with abnormal and detrimental consequences.
Incomplete dominance	**Inheritance:** This pattern occurs when the heterozygote has a phenotype that is intermediate between either corresponding homozygote. For example, a plant produced from a cross between red-flowered and white-flowered parents will have pink flowers. **Molecular:** 50% of the protein encoded by two copies of the normal (i.e., wild-type) allele is not sufficient to produce the normal trait.
Codominance	**Inheritance:** This pattern occurs when the heterozygote expresses both alleles simultaneously. For example, in blood typing, an individual carrying the *A* and *B* alleles will have an AB blood type. **Molecular:** The codominant alleles encode proteins that function slightly differently from each other, and the function of each protein, in the heterozygote, affects the phenotype uniquely.
Overdominance	**Inheritance:** This pattern occurs when the heterozygote has a trait that is more beneficial than either homozygote. **Molecular:** Three common ways that heterozygotes may have benefits include: their cells may be resistant to infection by microorganisms, they may produce protein dimers with enhanced function, or they may produce proteins that function under a wider range of conditions.
Incomplete penetrance	**Inheritance:** This pattern occurs when a dominant phenotype is not expressed even though an individual carries a dominant allele. An example is an individual who carries the polydactyly allele but has a normal number of fingers and toes. **Molecular:** Even though a dominant gene may be present, the protein encoded by the gene may not exert its effects. This can be due to environmental influences or due to other genes that may encode proteins that counteract the effects of the protein encoded by the (seemingly) dominant allele.
Sex-influenced inheritance	**Inheritance:** This pattern refers to the impact of sex on the phenotype of the individual. Some alleles are recessive in one sex and dominant in the opposite sex. An example would be baldness in humans. **Molecular:** Sex hormones may regulate the molecular expression of genes. This can have an impact on the phenotypic effects of alleles.
Sex-limited inheritance	**Inheritance:** This refers to traits that occur in only one of the two sexes. An example would be breast development in mammals. **Molecular:** Sex hormones may regulate the molecular expression of genes. This can have an impact on the phenotypic effects of alleles. In this case, sex hormones that are primarily produced in only one sex are essential to produce a particular phenotype.

1. inheritance pattern of single genes

- Prevalent ***alleles*** in a population are termed **wild-type *alleles***
  - These typically encode proteins that
    - **Function normally.**
    - **Are made in the right amounts.**
- ***Alleles*** that have been altered by **mutation** are termed **mutant alleles**
  - These tend to be **rare** in natural populations.

1. inheritance pattern of single genes

- Genetic diseases are caused by **mutant *alleles***.
- In many human genetic diseases , the **recessive *allele*** contains a mutation.
  - This prevents the ***allele*** from producing a fully functional **protein**

TABLE 4.2

Examples of Recessive Human Diseases

Disease	Protein That Is Produced by the Normal Gene*	Description
Phenylketonuria	Phenylalanine hydroxylase	Inability to metabolize phenylalanine. The disease can be prevented by a phenylalanine-free diet. If the diet is not followed early in life, symptoms can develop, including severe mental retardation and physical degeneration.
Albinism	Tyrosinase	Lack of pigmentation in the skin, eyes, and hair.
Tay-Sachs disease	Hexosaminidase A	Defect in lipid metabolism. Leads to paralysis, blindness, and early death.
Sandhoff disease	Hexosaminidase B	Defect in lipid metabolism. Muscle weakness in infancy, early blindness, and progressive mental and motor deterioration.
Cystic fibrosis	Chloride transporter	Inability to regulate ion balance across epithelial cells. Leads to production of thick lung mucus and chronic lung infections.
Lesch-Nyhan syndrome	Hypoxanthine-guanine phosphoribosyl transferase	Inability to metabolize purines, which are bases found in DNA and RNA. Leads to self-mutilation behavior, poor motor skills, and usually mental retardation and kidney failure.

*Individuals who exhibit the disease are homozygous (or hemizygous) for a recessive allele that results in a defect in the amount or function of the normal protein.

Inheritance pattern of single genes

- In a simple **dominant/recessive** relationship, the **recessive** allele **DOES NOT** affect the phenotype of the **heterozygote**.
  - So how can the wild-type phenotype of the heterozygote be explained?
- A **completely dominant allele** creates the full phenotype by one of two methods:
  - It produces half the amount of protein found in a homozygous dominant individual, but that is sufficient to produce the full phenotype. These genes are haplosufficient
  - Expression of the one active allele may be upregulated, generating protein levels adequate to produce the full phenotype

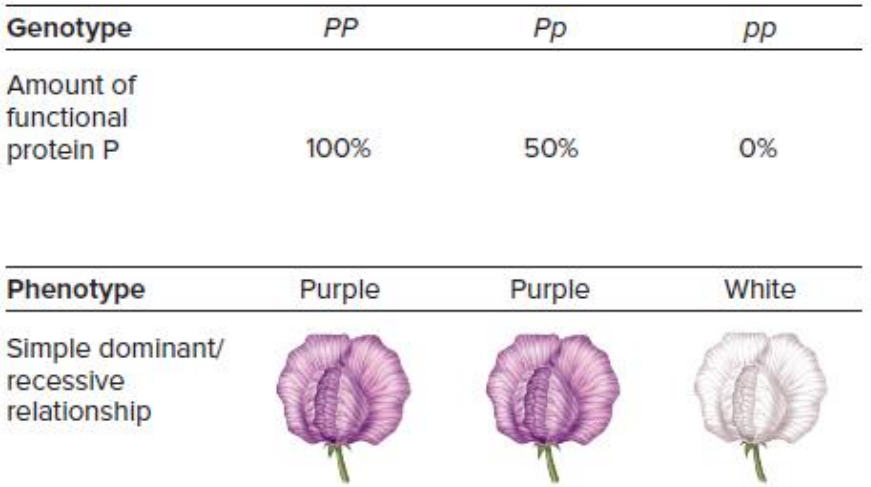


FIGURE A comparison of protein levels among homozygous (*PP* or *pp*) and heterozygous (*Pp*) genotypes.

Genes→Traits In a simple dominant/recessive relationship, 50% of the protein coded by one copy of the dominant allele in the heterozygote is sufficient to produce the wild-type phenotype, in this case, purple flowers. A complete lack of the functional protein results in white flowers.

Degrees of Dominance

- **Complete dominance** occurs when phenotypes of the heterozygote and dominant homozygote are identical
- In **incomplete dominance** when the phenotype of the heterozygote is intermediate (falls within the range) between the phenotypes of the two homozygotes.
- In **codominance**, two dominant alleles affect the phenotype in separate, distinguishable ways
  - Both alleles make a product, producing a combined phenotype

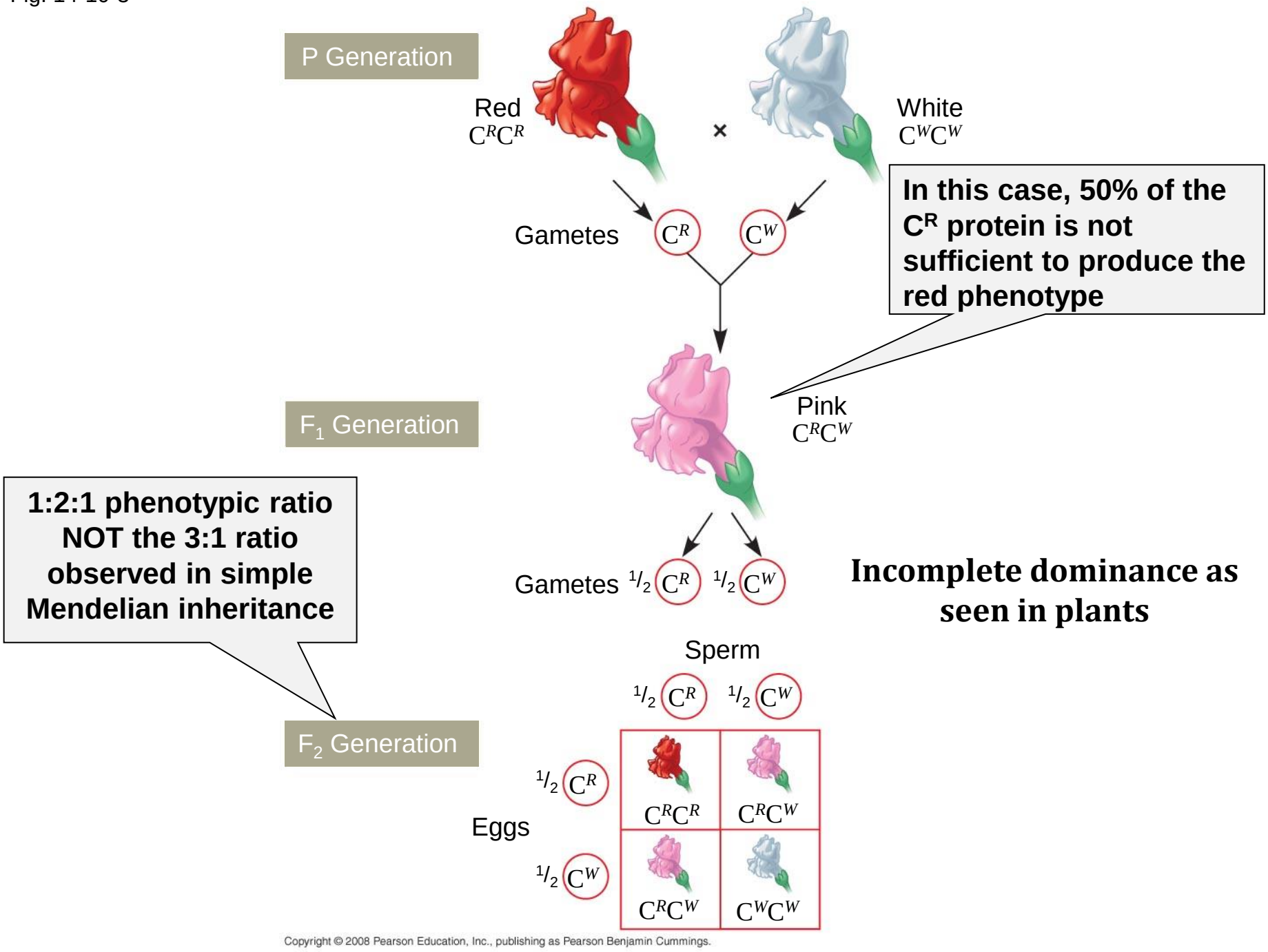
Incomplete Dominance

- In **incomplete dominance**, the recessive allele is not expressed, and the dominant allele produces only enough product for an intermediate phenotype

- Example: Flower color in four-o'clock plant is an example of incomplete dominance
  - Two alleles
    - C^R = wild-type allele for **red** flower color
    - C^W = allele for **white** flower color

Crosses of pure-breeding **red** with pure-breeding **white** results in <u>all</u> **pink** F_1 progeny

Fig. 14-10-3



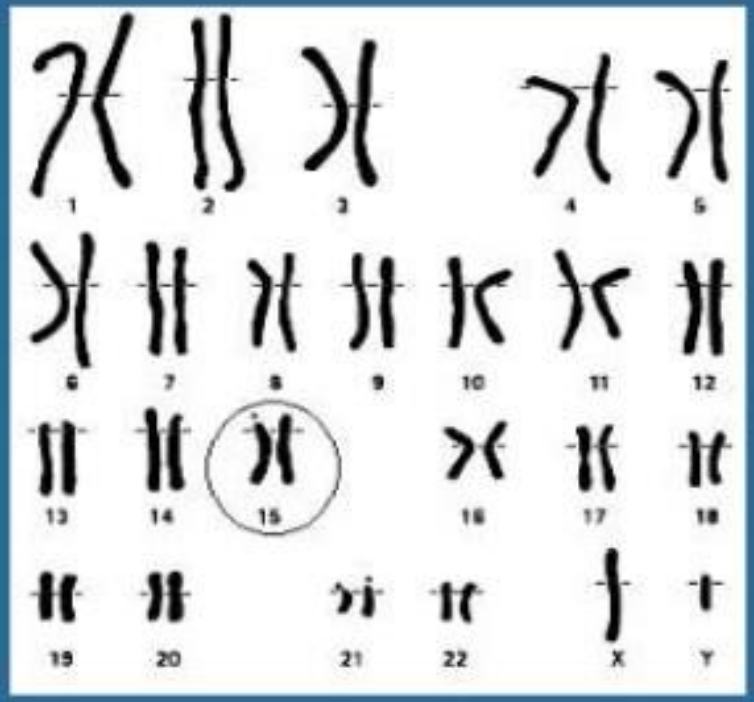
Incomplete dominance

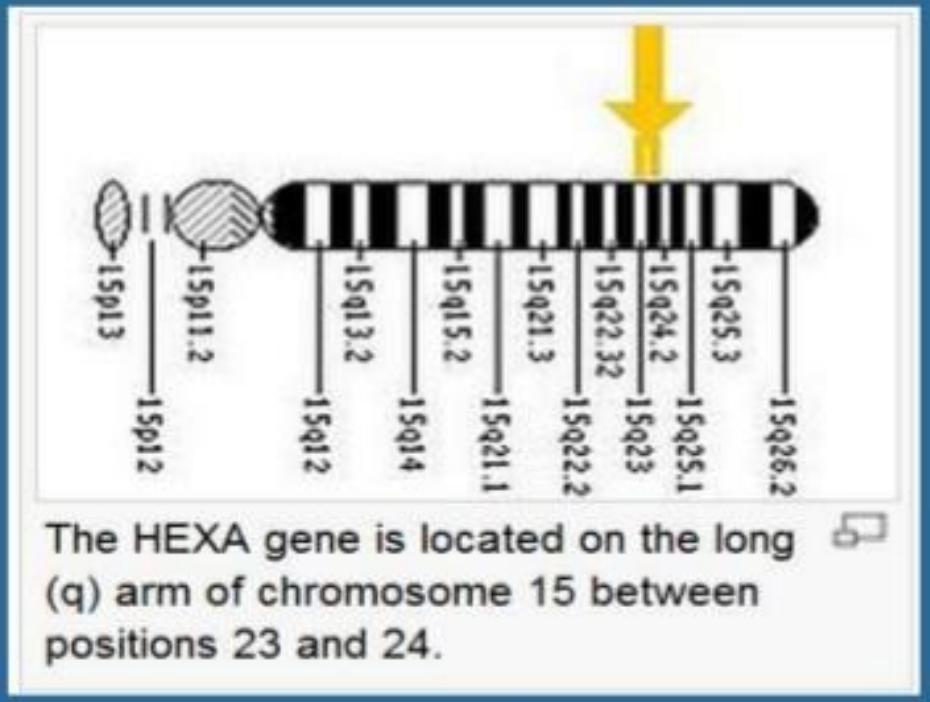
- The most well-studied example of incomplete dominance in humans occurs in the genes for curly hair.
- Inheriting a gene for curly hair from one parent and a gene for straight hair from the other parent will give a hair texture that is a blend of the two, wavy hair.

Homozygous Straight	Heterozygous	Homozygous Curly
hh	Hh	HH

Causes of Tay-Sachs

The disease is caused **by mutations on chromosome 15 in the HEX A gene,** which produces a lack of hexosaminidase A.





The HEXA gene is located on the long (q) arm of chromosome 15 between positions 23 and 24.

Tay Sach's features:

TAY SACHS

- **T**esting recommended
- **A**utosomal recessive
- **Y**oung death (<4 yrs.)
- **S**pot in macula (cherry red spots)
- **A**shkenazi Jews
- **C**NS degeneration
- **H**ex A deficiency
- **S**torage disease

MENDELIAN GENETICS AND HUMANS

Human genetic disorders

Tay Sachs Disease

Inheritance Pattern:

-Autosomal recessive

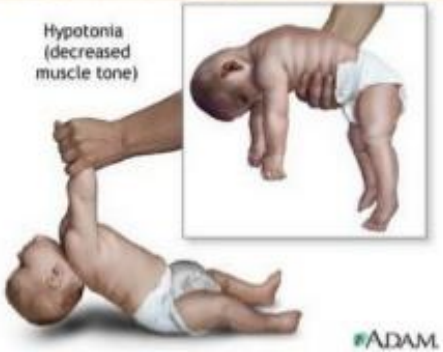
Physical Effects:

-Nerve cells destroyed in brain and spinal cord

-Symptoms appear 3-6 months after birth

-Loss of motor control and atrophy of muscles, seizures

-Death



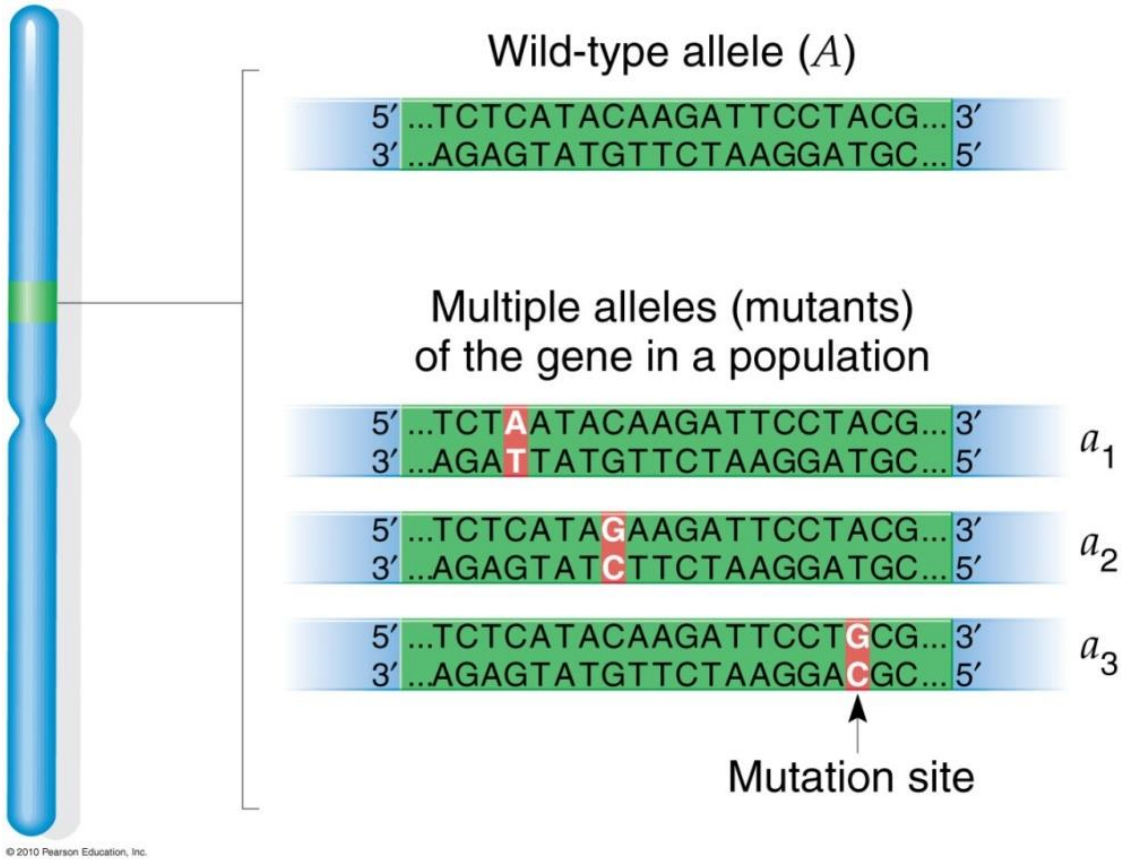
- **Tay-Sachs disease** is fatal; a dysfunctional enzyme causes an accumulation of lipids in the brain
  - At the *organismal* level, the allele is recessive
  - At the *biochemical* level, the phenotype (i.e., the enzyme activity level) is incompletely dominant
  - At the *molecular* level, the alleles are codominant

examples

- Human examples of *recessive lethal alleles*:
  - **Hemophilia:** results from an X-linked recessive allele and is lethal if untreated.
- A *dominant lethal gene* causes **Huntington disease**, characterized by progressive central nervous system degeneration. The phenotype is not expressed until individuals are in their 30's. Dominant lethals are rare, since death before reproduction would eliminate the gene from the pool

Multiple Alleles

- Although a gene only exists in two forms in an individual (alleles), many forms exist in a population (polymorphisms)



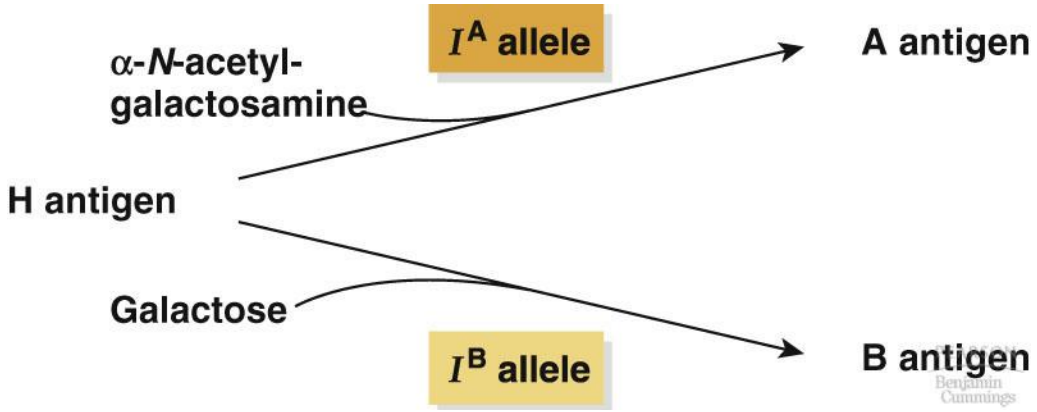
Multiple Alleles

- The **ABO blood group** provides another example of multiple alleles.
- It is determined by the type of antigen present on the surface of red blood cells.
  - Antigens are substances that are recognized by antibodies produced by the immune system

- There are three different types of antigens found on red blood
  - **Antigen A**, which is controlled by **allele I^A**
  - **Antigen B**, which is controlled by **allele I^B**
  - **Antigen O**, which is controlled by **allele *i***

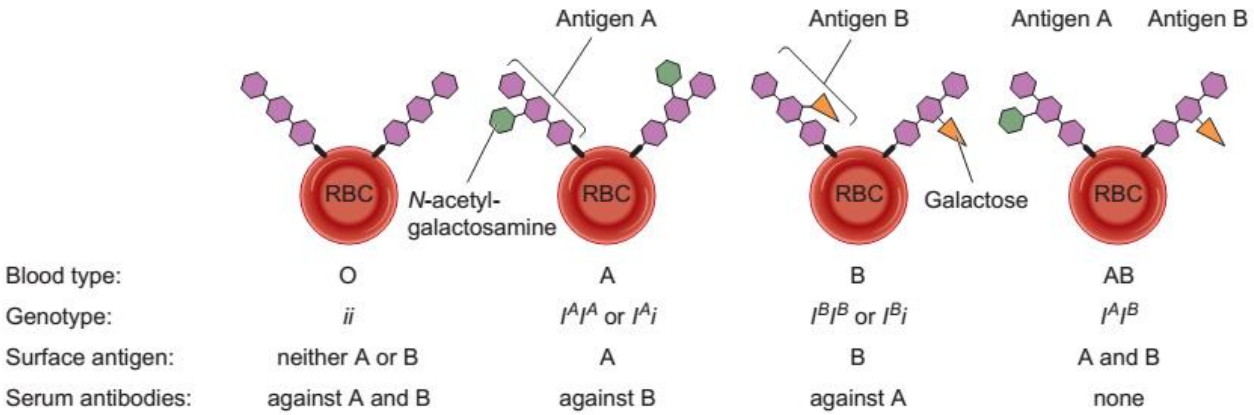
Biochemistry of ABO Red Blood Cell grouping

- The ABO locus produces RBC antigens by encoding glycosyltransferases, which add sugars to polysaccharides on membrane glycolipid molecules (the H antigen)
- Activity of the I^A gene product, α-N-acetylgalactosamyl transferase, converts the H antigen to the A antigen
- Activity of the I^B gene product, α-D-galactosyltransferase, converts the H antigen to the B antigen
- Neither enzyme is present in an *i/i* individual, and so the H antigen remains unmodified



Multiple Alleles

- Allele ***i*** is recessive to both I^A and I^B
- Alleles I^A and I^B are **codominant**
  - They are both expressed in a **heterozygous** individual

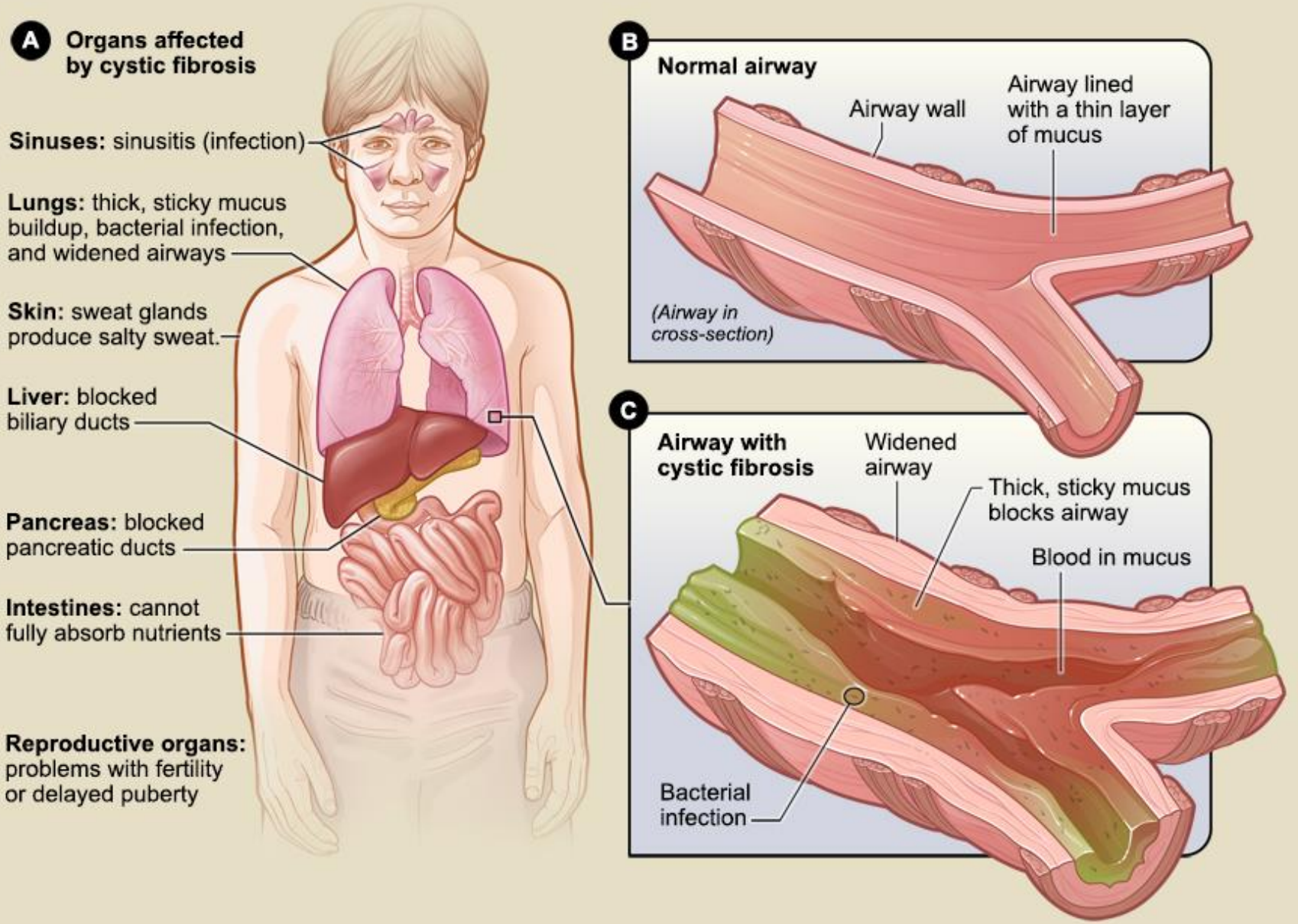


- A given gene may have more than two alleles, or multiple alleles; e.g. the series of alleles is denoted I^A, I^B ***and i***. However, each person carries only two of the alternatives $I^A I^A$, $I^B I^B$, $I^A I^B$, $I^A i$, $I^B i$, ii.
- allele is not inherently dominant or recessive; its dominance or recessiveness is always relative to a second allele.

Genotypes	Corresponding Phenotypes: Type(s) of Molecule on Cell
I^AI^A I^Ai	A
I^BI^B I^Bi	B
I^AI^B	AB
ii	O

Pleiotropy

- Most genes have multiple phenotypic effects, a property called **pleiotropy**
- For example, pleiotropic alleles are responsible for the multiple symptoms of certain hereditary diseases, such as cystic fibrosis
- Pleiotropy occurs for several reasons, including the following:
  - The expression of a single gene can affect cell function in more than one way. For example, a defect in a microtubule protein may affect cell division and cell movement.
  - A gene may be expressed in different cell types in a multicellular organism.
  - A gene may be expressed only at a specific stage of development.


A Organs affected by cystic fibrosis
Sinuses: sinusitis (infection)
Lungs: thick, sticky mucus buildup, bacterial infection, and widened airways
Skin: sweat glands produce salty sweat.
Liver: blocked biliary ducts
Pancreas: blocked pancreatic ducts
Intestines: cannot fully absorb nutrients
Reproductive organs: problems with fertility or delayed puberty
B
Normal airway
Airway wall
Airway lined with a thin layer of mucus
(Airway in cross-section)
C
Airway with cystic fibrosis
Widened airway
Thick, sticky mucus blocks airway
Blood in mucus
Bacterial infection

Summary of different dominance relationships

The phenotype of the heterozygote defines the dominance relationship of two alleles

Complete dominance: Hybrid resembles one of the two parents

Incomplete dominance: Hybrid resembles neither parent

Codominance: Hybrid shows traits from both parents

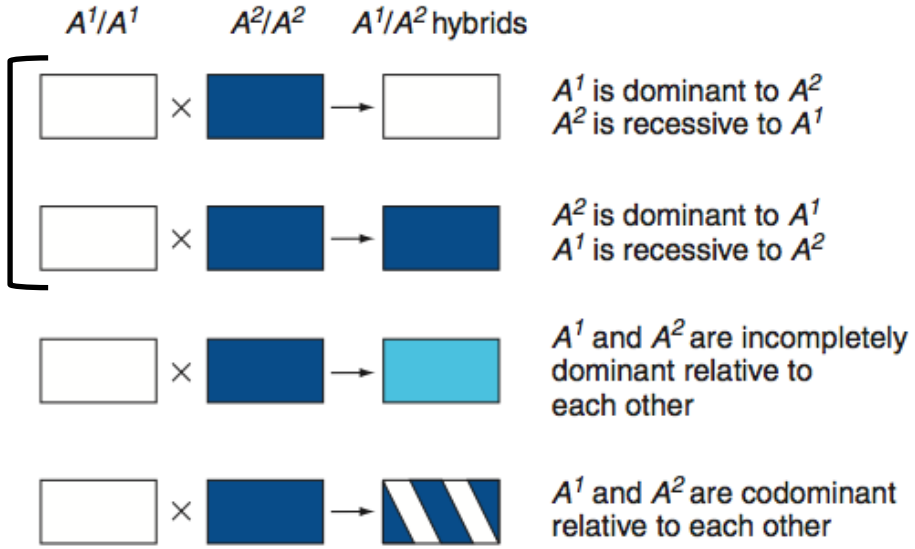


Figure 3.2

Overdominance

- **Overdominance** is the phenomenon in which a **heterozygote** is more vigorous than both of the corresponding **homozygotes**.
  - It is also called **heterozygote advantage.**
- Example = *Sickle-cell anemia*
  - **Autosomal recessive** disorder
  - Affected individuals produce abnormal form of hemoglobin
  - Two alleles
    - Hb^A → Encodes the **normal** hemoglobin, **hemoglobin A**
    - Hb^S → Encodes the **abnormal** hemoglobin, **hemoglobin S**

Overdominance

- $Hb^S Hb^S$ individuals have red blood cells that deform into a sickle shape under conditions of low oxygen tension.

  – This has two major complications

1. Sickling phenomenon greatly shortens the life span of the red blood cells

– Anemia results

2. Odd-shaped cells clump

– Partial or complete blocks in capillary circulation

  – Thus, affected individuals tend to have a shorter life span than unaffected ones

Overdominance

- The *sickle cell* ***allele*** has been found at a fairly high frequency in parts of Africa where malaria is found…!!!
  - How come?
- Malaria is caused by a protozoan, ***Plasmodium***
  - This parasite undergoes its life cycle in two main parts
    - One inside the *Anopheles* mosquito
    - The other inside **red blood** cells
  - Red blood cells of **heterozygotes**, are likely to rupture when infected by *Pasmodium sp*.
    - This **prevents** the propagation of the parasite
- Therefore, Hb^AHb^S individuals are "**better**" than
  - Hb^AHb^A, because they **do not** suffer from sickle cell anemia
  - Hb^SHb^S, because they are more resistant to malaria

Overdominance

- At the molecular level, overdominance is due to two alleles that produce slightly different proteins.

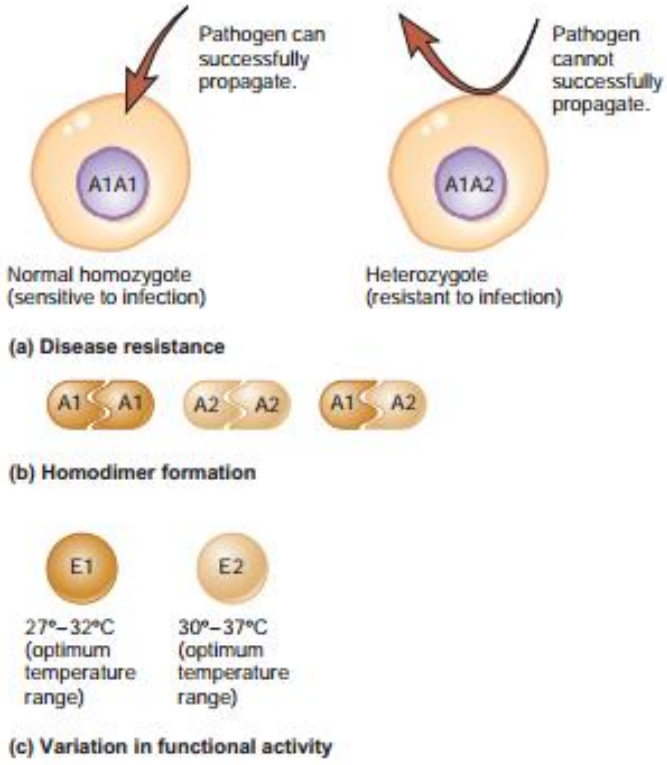
- **But how** can these two protein variants produce a favorable phenotype in the heterozygote?

- Well, there are **three possible explanations** for **overdominance** at the molecular/cellular level

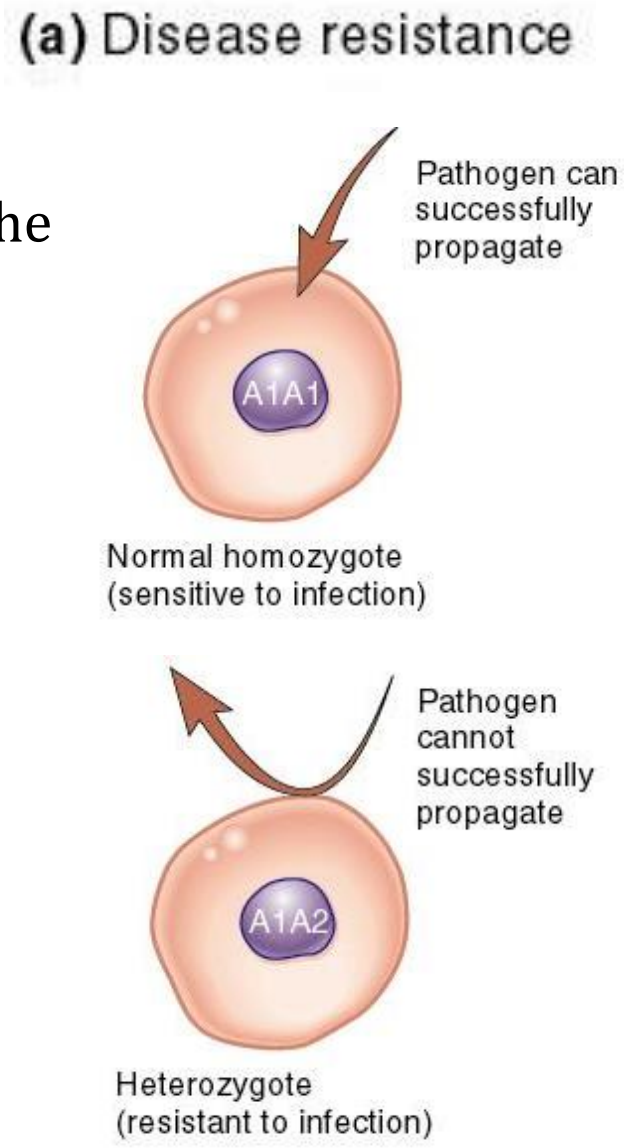
  a. **Disease resistance**

  b. **Homodimer formation**

  c. **Variation in functional activity**



- A microorganism will infect a cell if certain cellular proteins function optimally.
  - **Heterozygotes** have one altered copy of the gene.
  - Therefore, they have slightly reduced protein function.
  - This reduced function is **not enough** to cause serious side effects
  - But it is **enough to prevent infections.**
- Examples include
  - Sickle-cell anemia and malaria
  - Tay-Sachs disease
    - Heterozygotes are resistant to tuberculosis



- Some proteins function as **homodimers**
  - Composed of two different subunits
  - Encoded by two ***alleles*** of the same gene.
- ***A1A1*** homozygotes
  - Make only **A1A1 homodimers**
- ***A2A2*** homozygotes
  - Make only **A2A2 homodimers**
- ***A1A2* heterozygotes**
  - Make **A1A1** and **A2A2** homodimers and **A1A2** homodimers
- For some proteins, the **A1A2 homodimer** may have better functional activity
- Giving the **heterozygote superior characteristics**

(c) Variation in functional activity

- A gene, ***E***, encodes a metabolic ***enzyme***
- Allele ***E1*** encodes an ***enzyme*** that functions better at **lower** temperatures.
- Allele ***E2*** encodes an enzyme that functions better at **higher** temperatures
- ***E1E2*** heterozygotes produce **both** enzymes.
- Therefore they have an advantage under a wider temperature range than both ***E1E1*** and ***E2E2*** homozygotes

27°–32°C (optimum temperature range)

30°–37°C (optimum temperature range)

The same genotype does not always produce the same phenotype

- In all of the traits discussed so far, the relationship between a specific genotype and its corresponding phenotype has been absolute

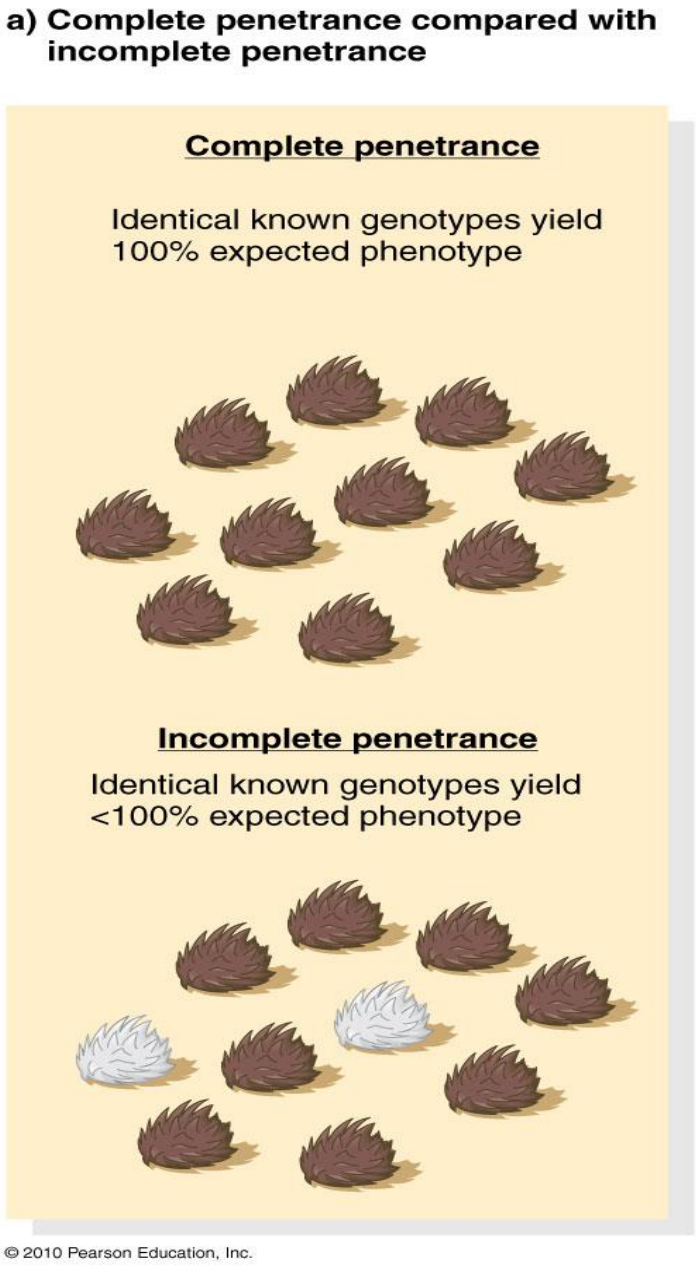
- Phenotypic variation for some traits can occur because of:
  - Differences in penetrance and/or expressivity
  - Effects of modifier genes
  - Effects of environment
  - Pure chance

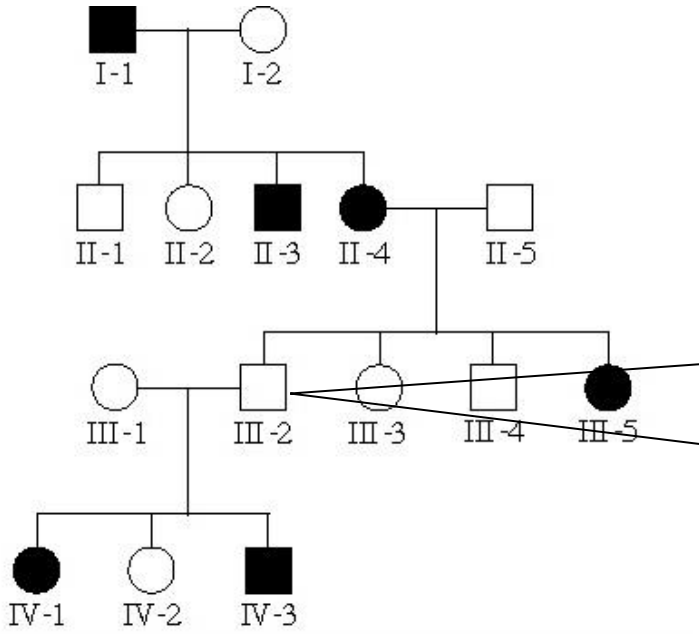
Incomplete Penetrance

- Penetrance is the percentage of a population with a particular genotype that shows the expected phenotype
- The term indicates that a **dominant *allele* does not** always "**penetrate**" into the phenotype of the individual.
  - Can be complete (100%) or incomplete (e.g. penetrance of retinoblastoma is 75%)
  - Incomplete penetrance, where an individual may carry a particular genotype but may not express the corresponding phenotype.
  - In any particular individual, the trait is either **penetrant** or **not**.
- The measure of **penetrance** is described at the **population** level.
  - If **60%** of **heterozygotes** carrying a dominant ***allele*** exhibit the trait ***allele***, the trait is **60% penetrant**.

Incomplete Penetrance

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





Inherited the polydactyly allele from his mother and passed it on to a daughter and son

Does not exhibit the trait himself even though he is a heterozygote

- Human examples include:
  - Brachydactyly involves abnormalities of the fingers, and shows 50–80% penetrance
  - Many cancer genes are thought to have low penetrance, making them harder to identify and characterize

Phenotype often depends on penetrance and/or expressivity

Penetrance is the percentage of a population with a particular genotype that shows the expected phenotype

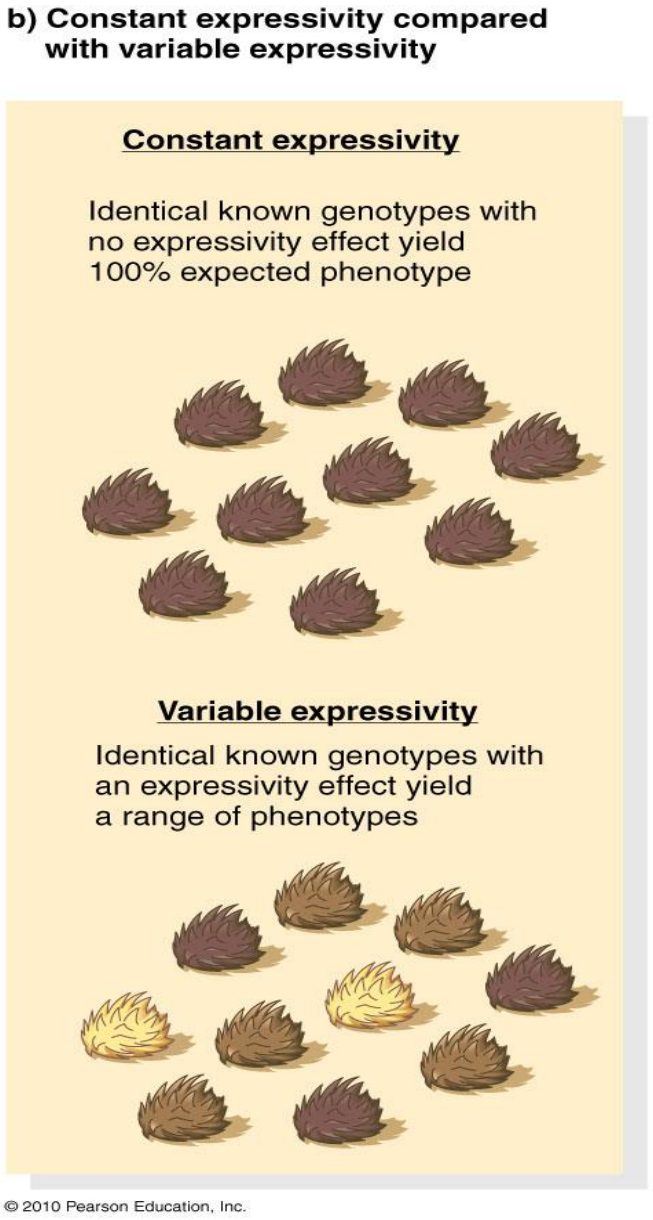
- Can be complete (100%) or incomplete (e.g. penetrance of retinoblastoma is 75%)

Expressivity is the degree or intensity with which a particular genotype is expressed in a phenotype

- Can be variable or unvarying

Expressivity

- **Expressivity** is the **degree** to which a trait is **expressed**.
- In the case of ***polydactyly***, the number of digits can **vary**.
- For example, one individual may have an extra toe on only one foot, whereas a second individual may have extra digits on both the hands and feet.
  - A person with ***several*** extra digits has **high** **expressivity**. of this trait.
  - A person with a ***single*** extra digit has **low** **expressivity**.

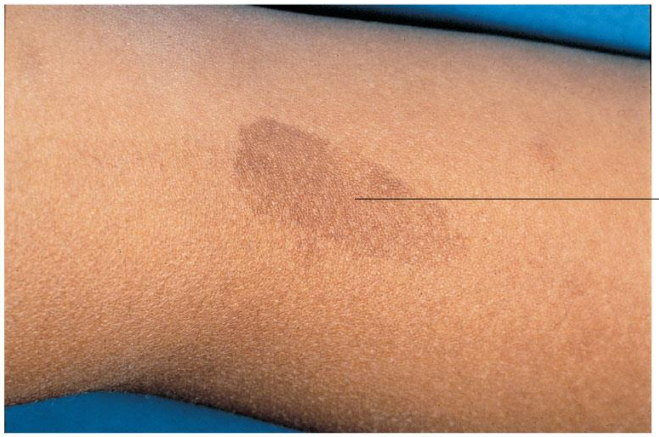


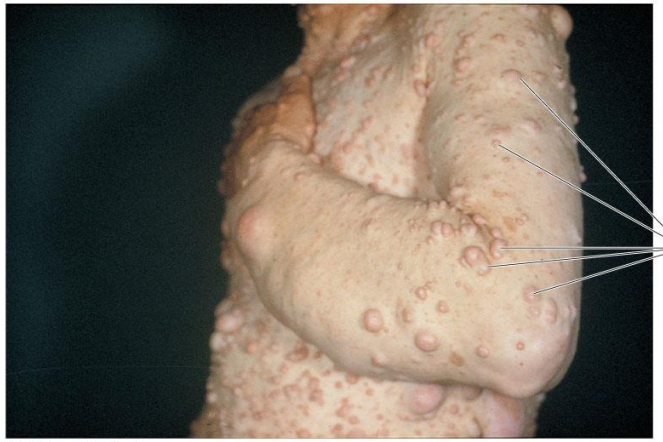
- Some genes have both **incomplete penetrance** and **variable expressivity**
  - Neurofibromatosis is an autosomal dominant disorder with 50-80% penetrance and variable expressivity
  - Individuals with the disease show a wide range of phenotypes
- Incomplete penetrance and variable expressivity complicate medical genetics and counseling

c) Incomplete penetrance with variable expressivity

Incomplete penetrance with variable expressivity

Identical known genotypes produce a broad range of phenotypes, due to varying degrees of gene activation and expression





Expressivity

- The molecular explanation of **expressivity** and **incomplete penetrance** may **not** always be understood.

- In most cases, the range of phenotypes is thought to be due to influences of the
  - **Environment**

    and/or
  - **Other genes**

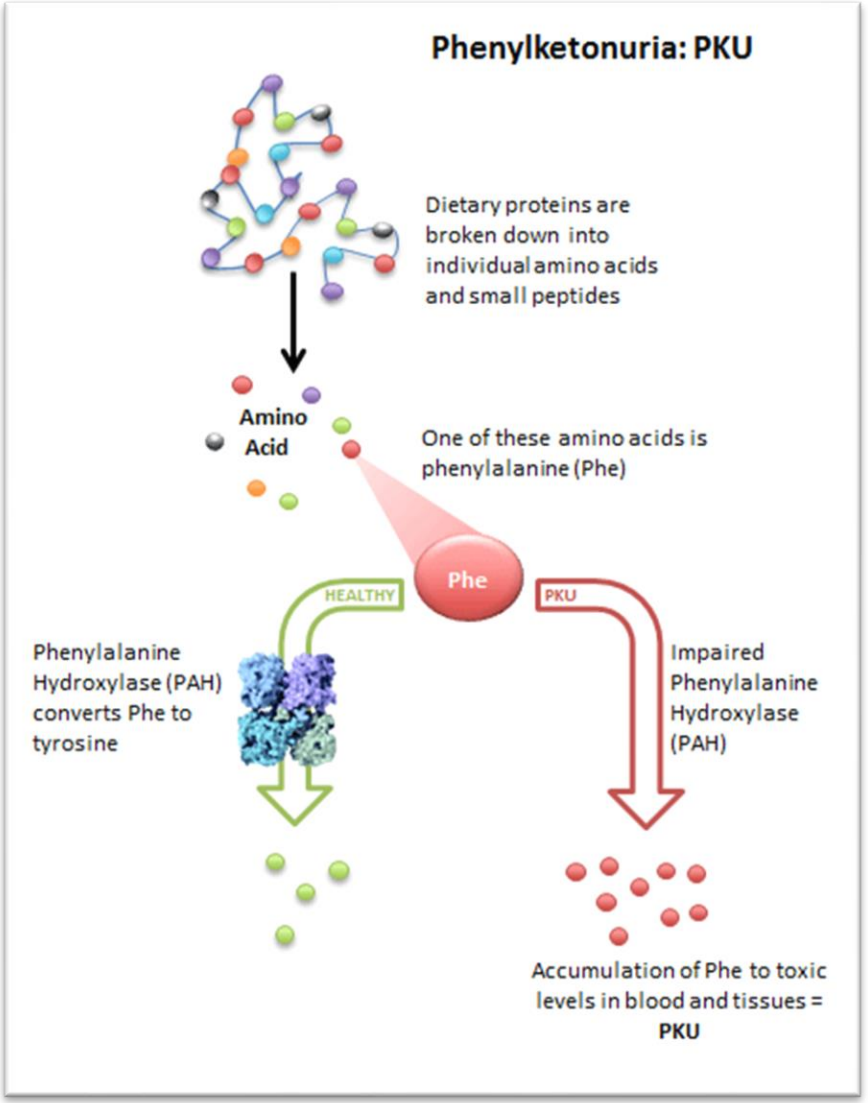
Environment

- **Environmental** conditions may have a great impact on the phenotype of the individual
- Temperature is a common element of the environment that can affect phenotype

- Example 1
  - The **arctic fox** (Alopex lagopus) goes through two color phases.
  - During the **cold** winter, the arctic fox is primarily **white**, but in the warmer summer, it is mostly **brown**.
  - Such **temperature sensitive** ***alleles*** affecting fur color are found among many species of mammals.

Environment

- Example 2 = Phenylketonuria
  - Autosomal recessive disorder in humans.
  - Caused by a defect in the gene that encodes the *enzyme phenylalanine hydroxylase*.
  - Affected individuals cannot metabolize *phenylalanine*.
    - *Phenylalanine* will thus accumulate in tissues especially brain



Environment

It ultimately causes a number of detrimental effects

- Mental retardation
- Delayed cognitive development
- Psychiatric disorders: Behavioral, emotional and social problems
- Neurological problems possibly leading to seizures
- Hyperactivity
- ⬇ Bone density
- Bad breath, urine odor, due to increase phenylalanine level
- Light skin, blue eyes due to obstruction in phenylalanine transforming to melanin.

- Newborns are now routinely screened for **PKU**.
- Individuals with the disease are put on a strict dietary regimen.
  - Their diet is essentially ***phenylalanine-free***.
- These individuals tend to develop normally
- Thus the **PKU** test prevents a great deal of human suffering
  - Furthermore, it is cost-effective

Effects of the Environment

- **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:
    - Pattern baldness, appearing in males aged 20–30 years
    - Duchenne muscular dystrophy, appearing in children aged 2 to 5 years

- **Sex** of the individual affects the expression of some autosomal genes
  - Sex-limited traits can appear in one sex but not the other
    - Examples include:
      - Milk production in dairy cattle, where both sexes have milk genes, but only females express them
      - In human?
  - 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
    - Examples include:
      - Pattern baldness, controlled by an autosomal gene that is dominant in males and recessive in females

Genotype	Phenotype in Females	Phenotype in Males
BB	**bald**	**bald**
Bb	**non**bald	**bald**
bb	**non**bald	**non**bald

      - Cleft lip and palate (2:1 ratio of males to females)
      - Other?