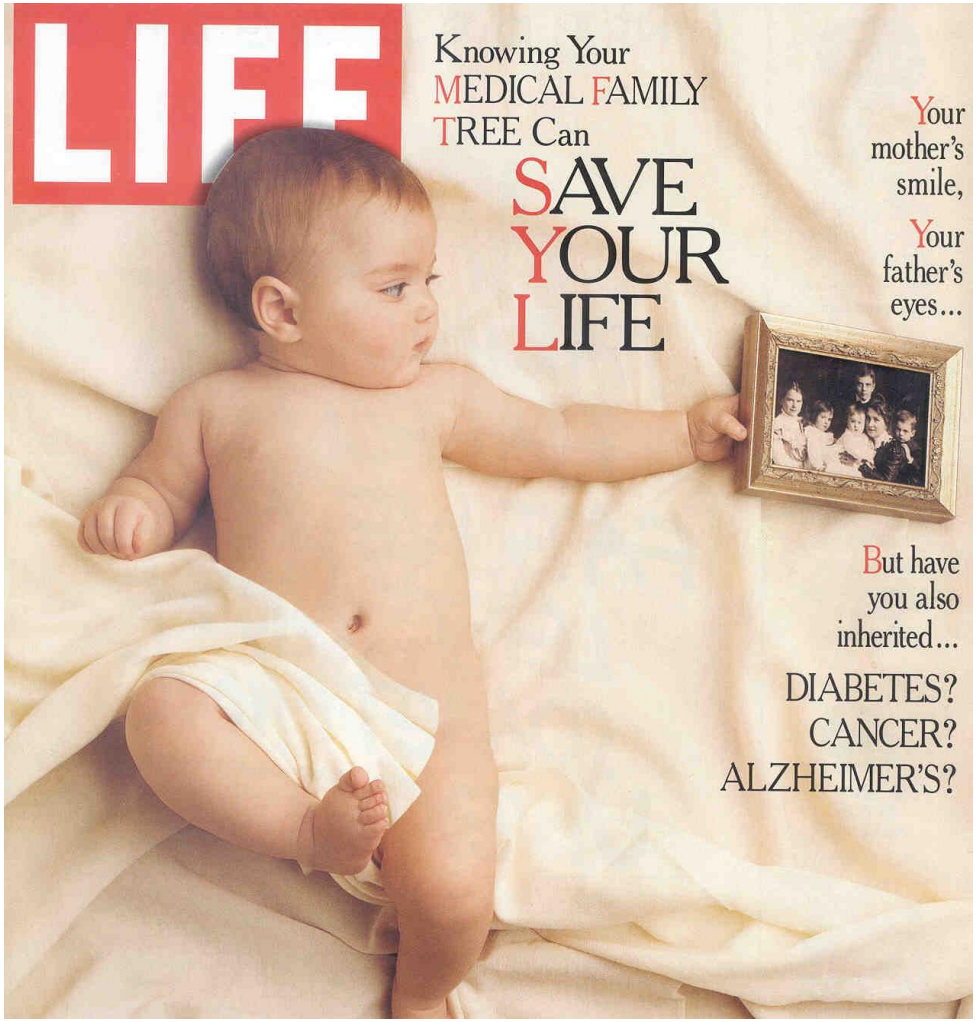
Single-Gene Inheritance

Importance of Family History



- Understanding the past is the key to predicting the future.

OBJECTIVES

- Construct and interpret pedigrees using standard nomenclature
- Describe the general features of Mendelian patterns of single gene inheritance.
- Identify the mode of inheritance of traits discussed in lecture.
- Describe aspects of phenotypic expression, using traits discussed in lecture as examples.
- Understand basic concepts of probability.
- Recognize the pattern of inheritance of a trait segregating in a family.
- Apply basic concepts of probability and principles of Mendelian inheritance to calculate the probabilities that offspring of specified mating types will be affected and unaffected.

Concept 14.3: Inheritance patterns are often more complex than predicted by simple Mendelian genetics

- The relationship between genotype and phenotype is rarely as simple as in the pea plant characters Mendel studied
- Many heritable characters are not determined by only one gene with two alleles
- However, the basic principles of segregation and independent assortment apply even to more complex patterns of inheritance

Extending Mendelian Genetics for a Single Gene

- Inheritance of characters by a single gene may deviate from simple Mendelian patterns in the following situations:
  - When alleles are not completely dominant or recessive
  - When a gene has more than two alleles
  - When a gene produces multiple phenotypes

Degrees of Dominance

- Each gene has two alleles, with one allele inherited from each parent.

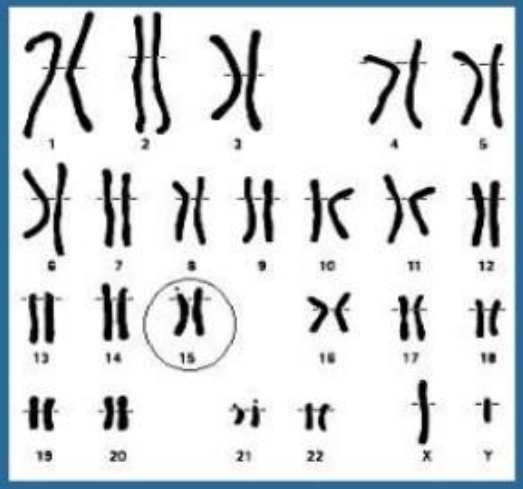
- **Complete dominance** occurs when phenotypes of the heterozygote and dominant homozygote are identical
  - ✓ If one allele is dominant over the other, this is referred to as **complete dominance.**
- In **incomplete dominance**, the phenotype of F_1 hybrids is somewhere between the phenotypes of the two parental varieties
- In **codominance**, two dominant alleles affect the phenotype in separate, distinguishable ways

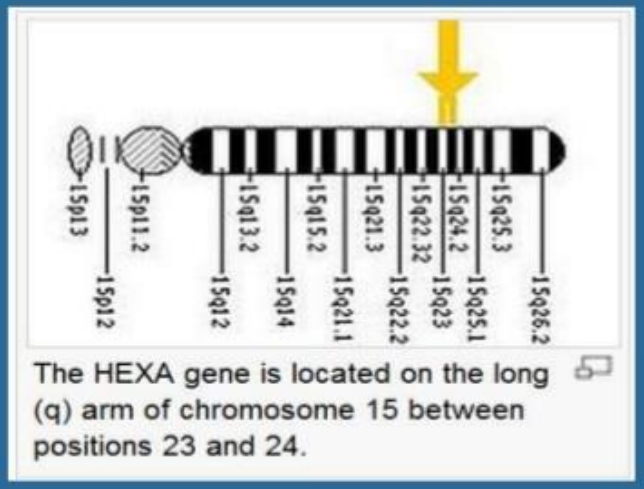
The Relation Between Dominance and Phenotype

- A dominant allele does not subdue a recessive allele; alleles don't interact that way
- Alleles are simply variations in a gene's nucleotide sequence
- For any character, dominance/recessiveness relationships of alleles depend on the level at which we examine the phenotype

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.

This gene encodes an enzyme involved in lipid metabolism.

- This disease follows a **recessive** mode of inheritance.
- **Both alleles** of the gene must be **mutated** and dysfunctional for the individual to be affected.
- If one allele is normal (dominant) and the other allele is mutated, the normal allele compensates, and the individual remains unaffected.

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

Because the enzyme is defective, lipid metabolism does not occur properly, leading to **lipid accumulation** in the brain and resulting in central nervous system damage.

MENDELIAN GENETICS AND HUMANS

Human genetic disorders

Tay Sachs Disease

Inheritance Pattern:

-Autosomal recessive

Physical Effects:

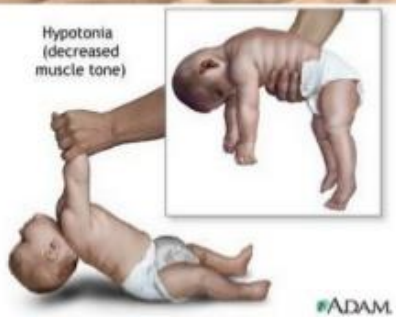
-Nerve cells destroyed in brain and spinal cord

-Symptoms appear 3-6 months after birth

-Loss of motor control and atrophy of muscles, seizures

+ Hypotonia

-Death



Autosomal Recessive Disorders

- Tay-Sachs Disease
  - Usually occurs in Jewish people
  - Symptoms
    - Development slows at age 4 to 8 months
    - Neurological and Psychomotor impairment
    - Child gradually becomes blind and helpless, seizures, paralyzed, death by age 3 – 4 years old
  - Caused by gene on chromosome 15 → caused buildup of nonfunctional lysosomes in neurons

- **Tay-Sachs disease** is fatal; a dysfunctional enzyme causes an accumulation of lipids in the brain
  - At the *organismal* level, the allele is **recessive** (both alleles must be mutated for the disease to manifest). A wild type (normal) allele is completely dominant over a mutant allele.
  - At the *biochemical* level, the phenotype (i.e., the enzyme activity level) is **incompletely dominant**
  - At the *molecular (genetic)* level, the alleles are **codominant**

- There are three possible scenarios:

1. **Homozygous wild type**: both alleles are normal.
2. **Homozygous mutant**: both alleles are mutated, and the individual is affected.
3. **Heterozygous**: one normal allele and one mutant allele; the individual is clinically normal ***but is a carrier***.

✓ *Degree of dominance may vary within the same disease. It depends on the **level** at which the system is analyzed.*

See the next slide

➢ **Biochemical level:**

- A gene encodes an enzyme, and the enzyme functions to catalyze (speed up) a chemical reaction.
- ✓ In a ***homozygous wild type individual*** (two normal alleles), both alleles produce functional protein (functional enzyme), resulting in **100% biochemical activity.**
- ✓ In a ***homozygous mutant individual*** (both alleles mutated), no functional enzyme is produced, resulting in **0% biochemical activity.**
- ✓ If an ***individual is heterozygous***, one allele is transcribed and translated into a functional enzyme, while the other mutated allele is transcribed and translated into a non-functional enzyme for the same gene.
- The heterozygous individual produces both functional and dysfunctional enzyme products.
- If biochemical activity is measured, enzyme activity in heterozygotes lies **between 0% and 100%**. This intermediate biochemical activity is considered ***incomplete dominance.***

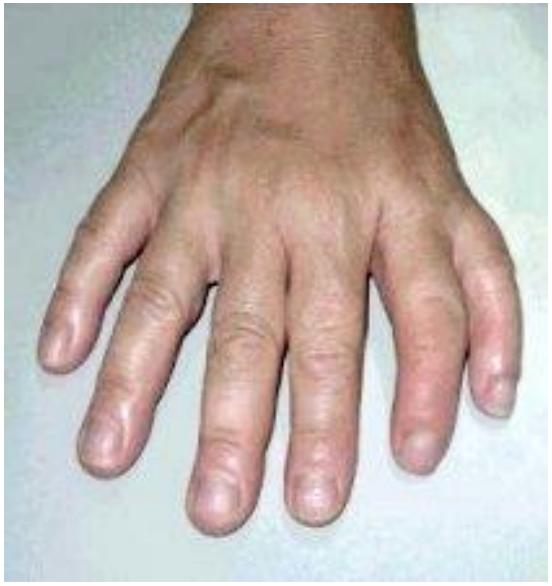
➢ **Molecular (genetic) level:**

- In heterozygous individuals, two alleles are present: one normal allele and one mutant allele.
- Each allele undergoes gene expression independently, as RNA polymerase binds to each allele, allowing both alleles to be transcribed and translated.
- The normal allele produces a functional enzyme, whereas the mutant allele produces a dysfunctional enzyme.
- At the molecular level, both alleles are expressed; therefore, this situation is considered ***codominance***, since both alleles are actively expressed.

Frequency of Dominant Alleles

- Dominant alleles are not necessarily more common in populations than recessive alleles
- For example, Polydactyly one baby out of 400 in the United States is born with extra fingers or toes

  - A dominant allele causing extra digits (polydactyly) is **less prevalent** than the recessive allele associated with the normal number of digits.



- The allele for this unusual trait is dominant to the allele for the more common trait of five digits per appendage
- In this example, the recessive allele is far more prevalent than the population's dominant allele

Multiple Alleles

- Most genes exist in populations in more than two allelic forms
- For example, the four phenotypes of the **ABO blood group** in humans are determined by *three alleles* for the enzyme (I) that attaches A or B carbohydrates to red blood cells: I^A, I^B, and *i*.
- The enzyme encoded by the I^A allele adds the A carbohydrate, whereas the enzyme encoded by the I^B allele adds the B carbohydrate; the enzyme encoded by the *i* allele adds neither

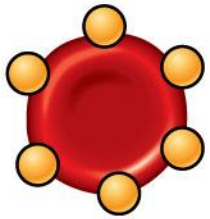
- On the population level, multiple alleles may exist for a gene (e.g., three or more alleles in the population).
- On the individual level, each autosomal gene is present as **two alleles**, one inherited from each parent, *except for genes located on the sex chromosomes in males.*

Figure 14.11

(a) The three alleles for the ABO blood groups and their carbohydrates

Allele	I^A	I^B	i
Carbohydrate	A 	B 	none

(b) Blood group genotypes and phenotypes

Genotype	Dominant allele I^AI^A or I^Ai	Dominant allele I^BI^B or I^Bi	I^AI^B	ii
Red blood cell appearance				
Phenotype (blood group)	A	B	AB Heterozygous for alleles A and B	O Homozygous for allele i

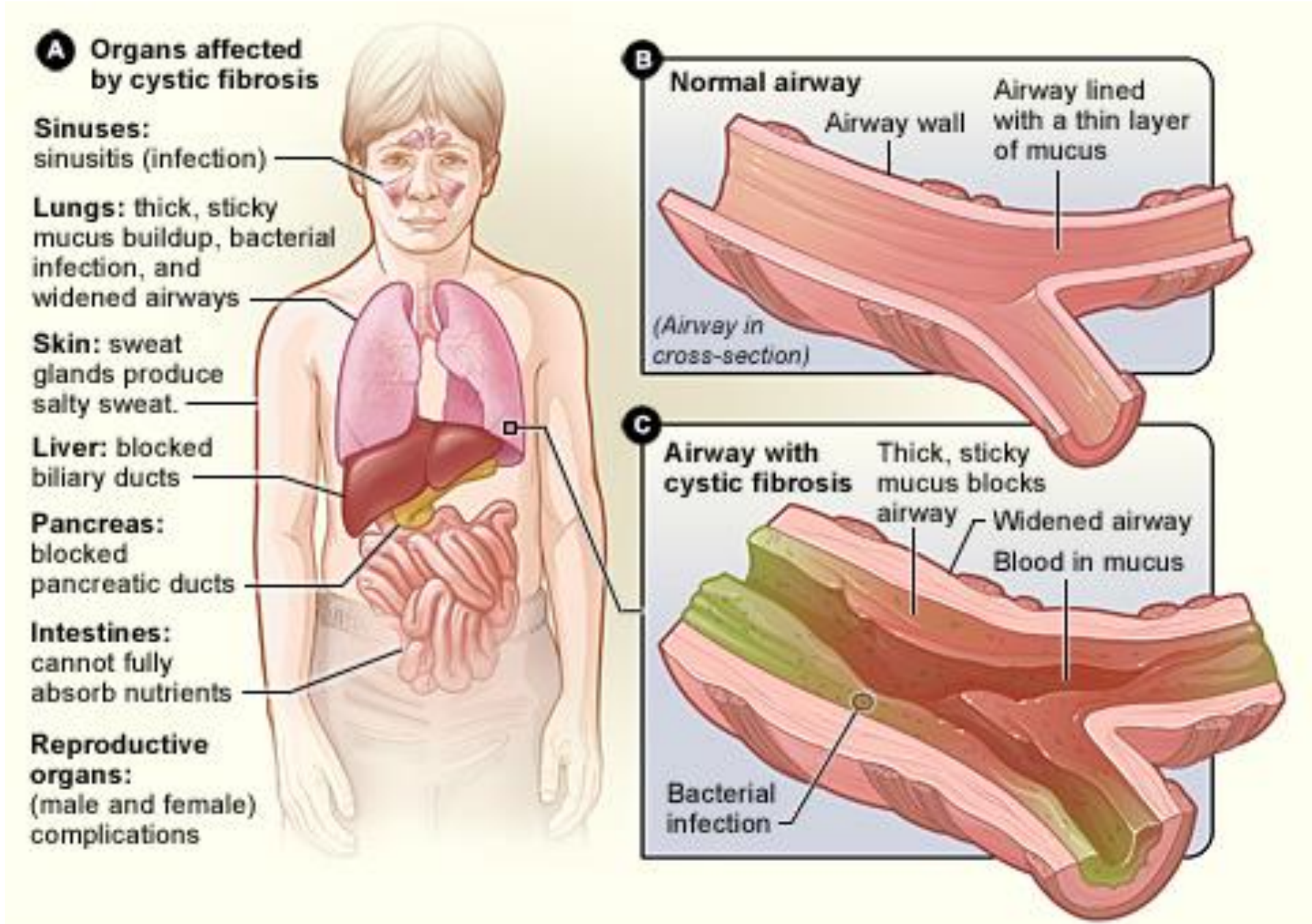
Pleiotropy

✓ Single gene with multiple phenotypic effects.

- 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 and sickle-cell disease

  - Cystic fibrosis is caused by mutations in the **CFTR gene,** which is inherited in an **autosomal recessive** manner.
  - When both alleles are mutated, chloride ion transport across the cell membrane is impaired due to dysfunction of the chloride channel. As a result, chloride transport is disrupted, leading to **accumulation of thick mucus** in body cavities and the respiratory airways.

Important


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: (male and female) complications
B Normal airway
Airway wall
Airway lined with a thin layer of mucus
(Airway in cross-section)
C Airway with cystic fibrosis
Thick, sticky mucus blocks airway
Widened airway
Blood in mucus
Bacterial infection

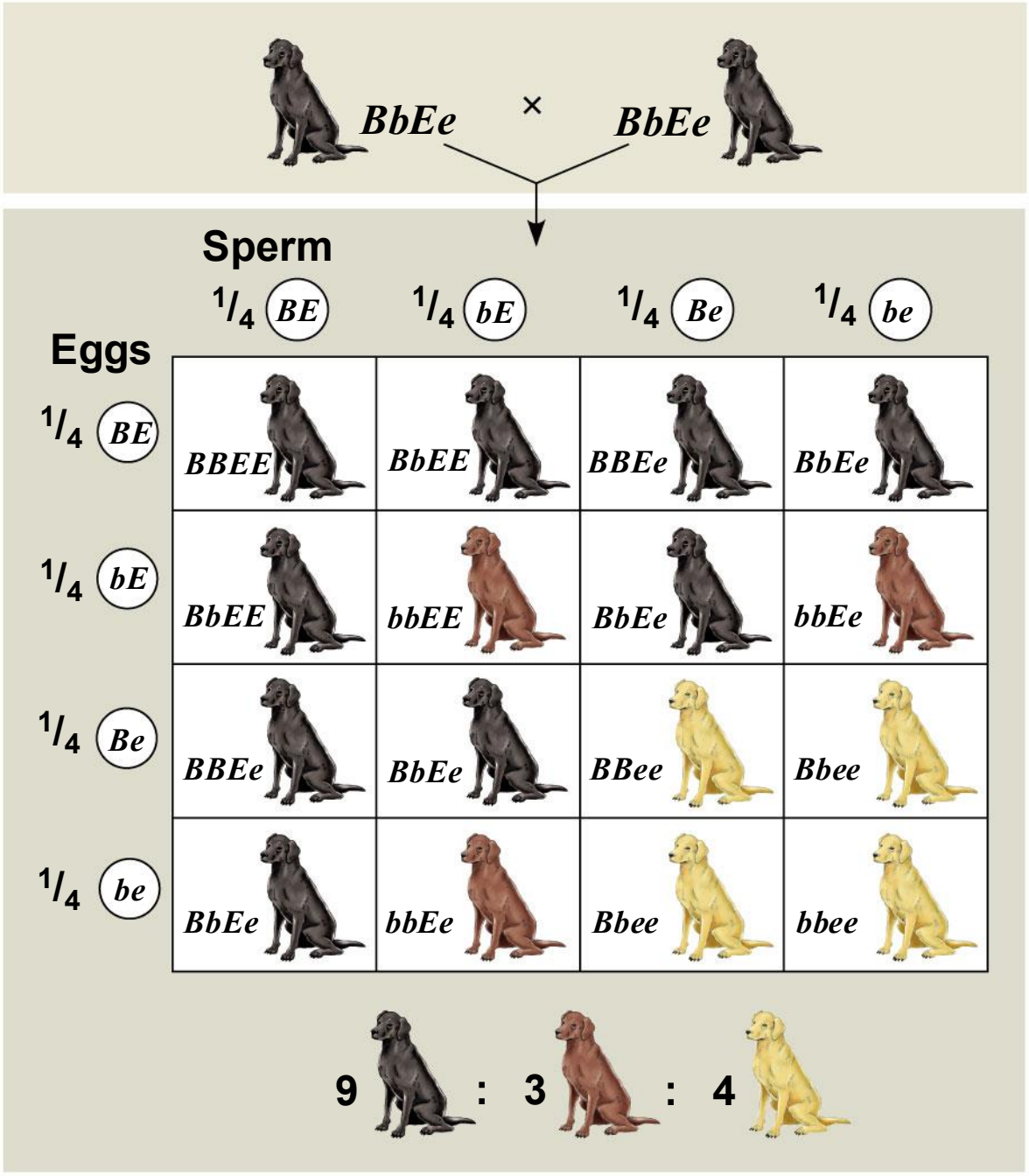
Extending Mendelian Genetics for Two or More Genes

- Some traits may be determined by two or more genes

Epistasis

- In **epistasis**, a gene at one locus alters the phenotypic expression of a gene at a second locus
- For example, in Labrador retrievers and many other mammals, **coat color** depends on two genes
- One gene determines the pigment color (with alleles *B* for black and *b* for brown)
- The other gene (with alleles *C* for color and *c* for no color) determines whether the pigment will be deposited in the hair

Figure 14.12



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❖ We have two genes: **gene B and gene E.**

➢ **Gene B** determines coat color:

- **BB** or **Bb** → **black** coat color (dominant phenotype).
- **bb** → **brown** coat color (recessive phenotype).

➢ There is another gene called **gene E**.

- When the genotype is **ee**, the coat color becomes white, regardless of the B gene genotype.

- The mutation in gene E prevents expression of the color controlled by gene B, so *neither black nor brown color appears*.

✓ Therefore, gene E has an **epistatic effect** over gene B (recessive epistasis).

Polygenic Inheritance

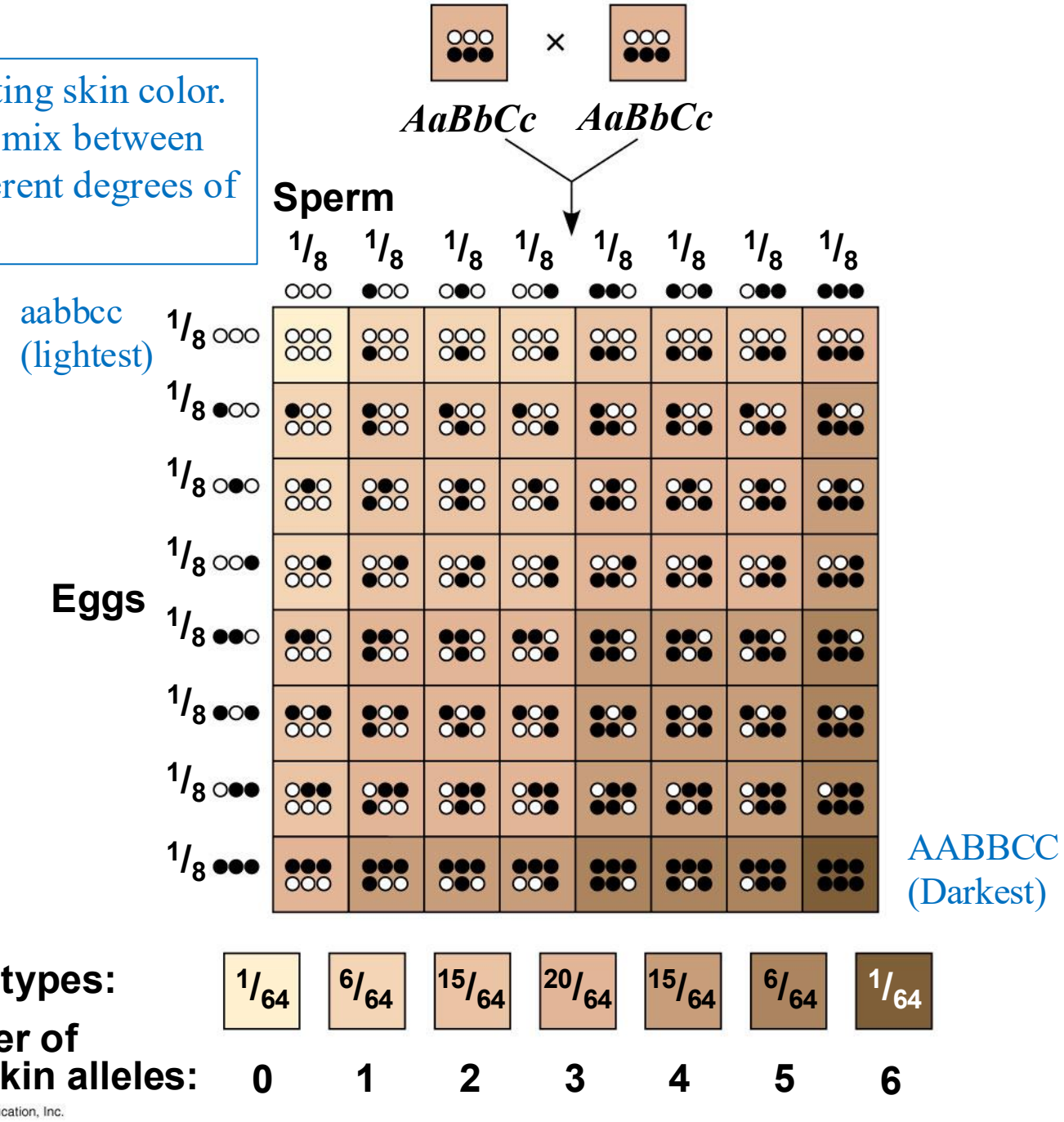
✓ A group of genes causing one phenotypic effect

- **Quantitative characters** are those that vary in the population along a continuum
- Quantitative variation usually indicates **polygenic inheritance**, an additive effect of two or more genes on a single phenotype
- Skin color in humans is an example of polygenic inheritance

  - **Examples**: DM, Hypertension, cancer, and many psychiatric disorders.

Figure 14.13

- **Three** genes impacting skin color.
- Any recombination mix between them results in different degrees of skin color.



Nature and Nurture: The Environmental Impact on Phenotype

- Another departure from Mendelian genetics arises when the phenotype for a character depends on environment as well as genotype
- The **norm of reaction** is the phenotypic range of a genotype influenced by the environment
- For example, hydrangea flowers of the same genotype range from blue-violet to pink, depending on soil acidity

- Norms of reaction are generally broadest for polygenic characters
- Such characters are called **multifactorial** because genetic and environmental factors collectively influence phenotype

- Most genetic diseases are **polygenic**.
- When environmental factors also influence the phenotype through gene–environment interaction, the condition is called a **multifactorial disorder.**
- Both genetic factors and environmental factors contribute to the development of the disease.

✓ An individual who has genetic susceptibility to diabetes and a positive family history, combined with obesity and high sugar intake, has a higher risk of developing diabetes compared to an individual with similar genetics who follows a low-sugar, low-carbohydrate diet and maintains a healthy weight.

Integrating a Mendelian View of Heredity and Variation

- An organism's phenotype includes its physical appearance, internal anatomy, physiology, and behavior
- An organism's phenotype reflects its overall genotype and unique environmental history

Concept 14.4: Many human traits follow Mendelian patterns of inheritance

- Humans are not good subjects for genetic research
  - Generation time is too long
  - Parents produce relatively few offspring
  - Breeding experiments are unacceptable
- However, basic Mendelian genetics endures as the foundation of human genetics

Pedigree Analysis

- A **pedigree** is a family tree that describes the interrelationships of parents and children across generations
- Inheritance patterns of particular traits can be traced and described using pedigrees

- Pedigrees can also be used to make predictions about future offspring
- We can use the multiplication and addition rules to predict the probability of specific phenotypes

Please click here and let me know if there's any mistake.
Good Luck ☺