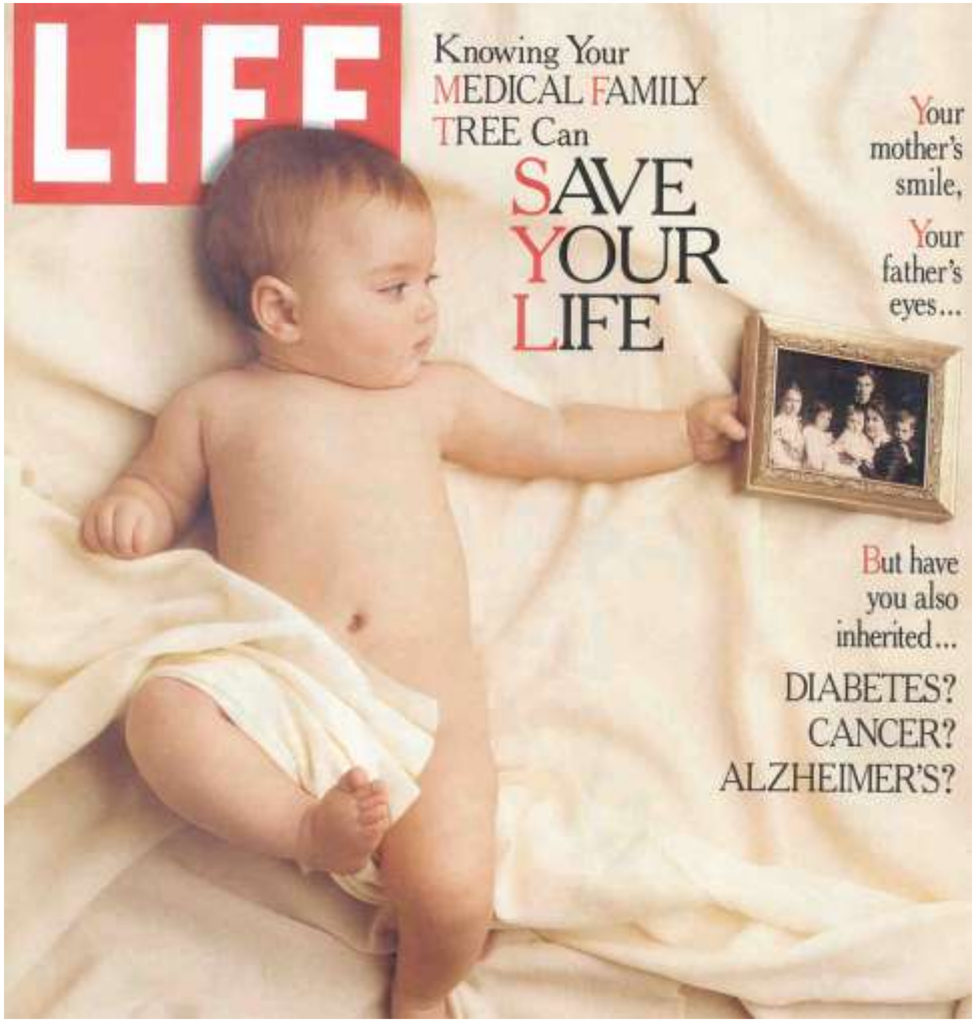
Single-Gene Inheritance

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

* Reminder:
each gene has 2 alleles, 1 from
each parent

- **Complete dominance** occurs when phenotypes of the heterozygote and dominant homozygote are identical ⇒ if one allele is dominant over the other.
- 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 (slide #11)

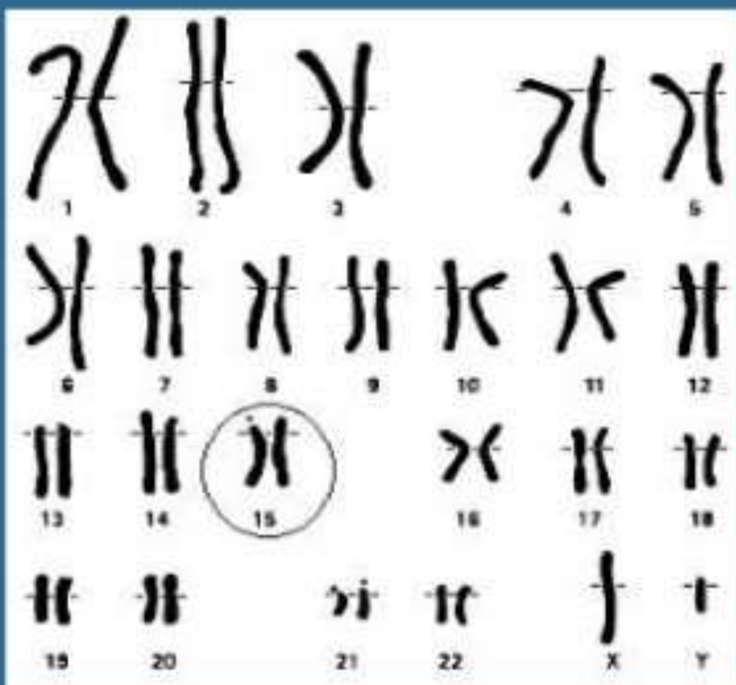
Causes of Tay-Sachs

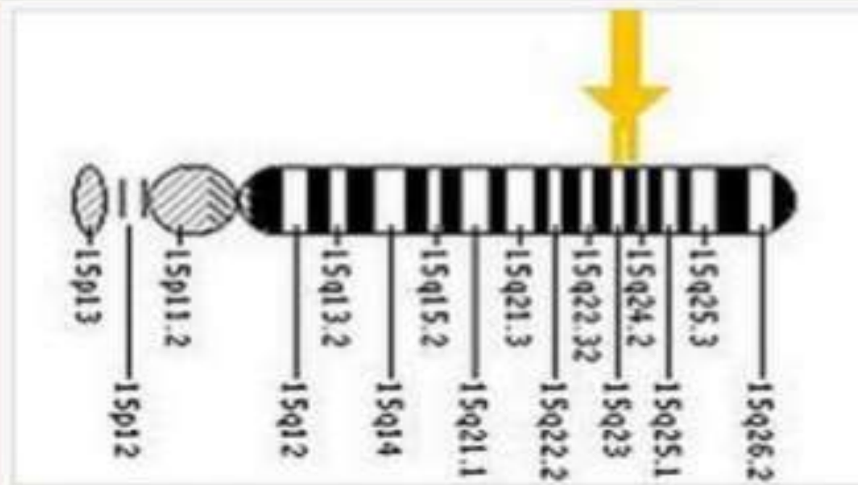
⇒ it is a recessive disease (both alleles of this gene are required to be mutated in order for the individual to be affected)

⇒ therefore the normal allele is dominant over the mutated allele.

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

↳ responsible of lipid metabolism.





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 → due to building up of lipids in the brain
- **H**ex A deficiency
- **S**torage disease

*Symptoms appear at the first few months of life.

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 (hypotonic)

-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 → heterozygote is asymptomatic
  - At the *biochemical* level, the phenotype (i.e., the enzyme activity level) is incompletely dominant
    - enzyme's biochemical activity
      - → homozygous wild-type = 100% (all enzymes expressed are normal)
      - → homozygous mutant = 0% (x functional enzymes)
      - → heterozygous = between 0-100% (some enzymes are normal)
  - At the *molecular* level, the alleles are codominant
    - → both alleles are expressed
      - → normal allele → functional enzyme
      - → mutated allele → dysfunctional enzyme

* 3 scenarios
- → homozygous wild-type (both alleles normal) → normal individual.
- → both alleles mutated → affected individual
- → heterozygous
  - → clinically : normal (carrier)
  - → molecular / genetic level: codominance (both alleles expressed)
  - → biochemical level : incomplete dominance.

→ Sometimes in the same disease it depends on the level we're looking at.

(if a question on Tay-Sachs does NOT ask about a specific level then answer recessive)

Frequency of Dominant Alleles

digits of hands & feet → extra digits: dominant allele. / → normal # of digits : recessive allele.

dominant allele (extra digits) is less prevelant than the recessive allele (normal #)

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

- 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

* on the individual level → each gene has 2 alleles.
• population level → each gene could have >2 alleles. (i.e: blood types)

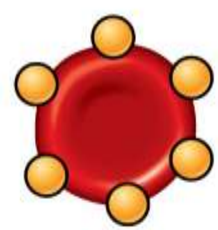
- Most genes exist in populations in more than two allelic forms
- For example, the four phenotypes of the ABO blood group in humans are determined by three alleles for the enzyme (I) that attaches A or B carbohydrates to red blood cells: I^A, I^B, and i.
  ↳ 3 alleles seen in the population (but on an individual level each gene has 2 alleles EXCEPT for the genes in the sex chromosome in males)
- 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

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	I^AI^A or I^Ai	I^BI^B or I^Bi	I^AI^B	ii
Red blood cell appearance				
Phenotype (blood group)	A	B	AB	O

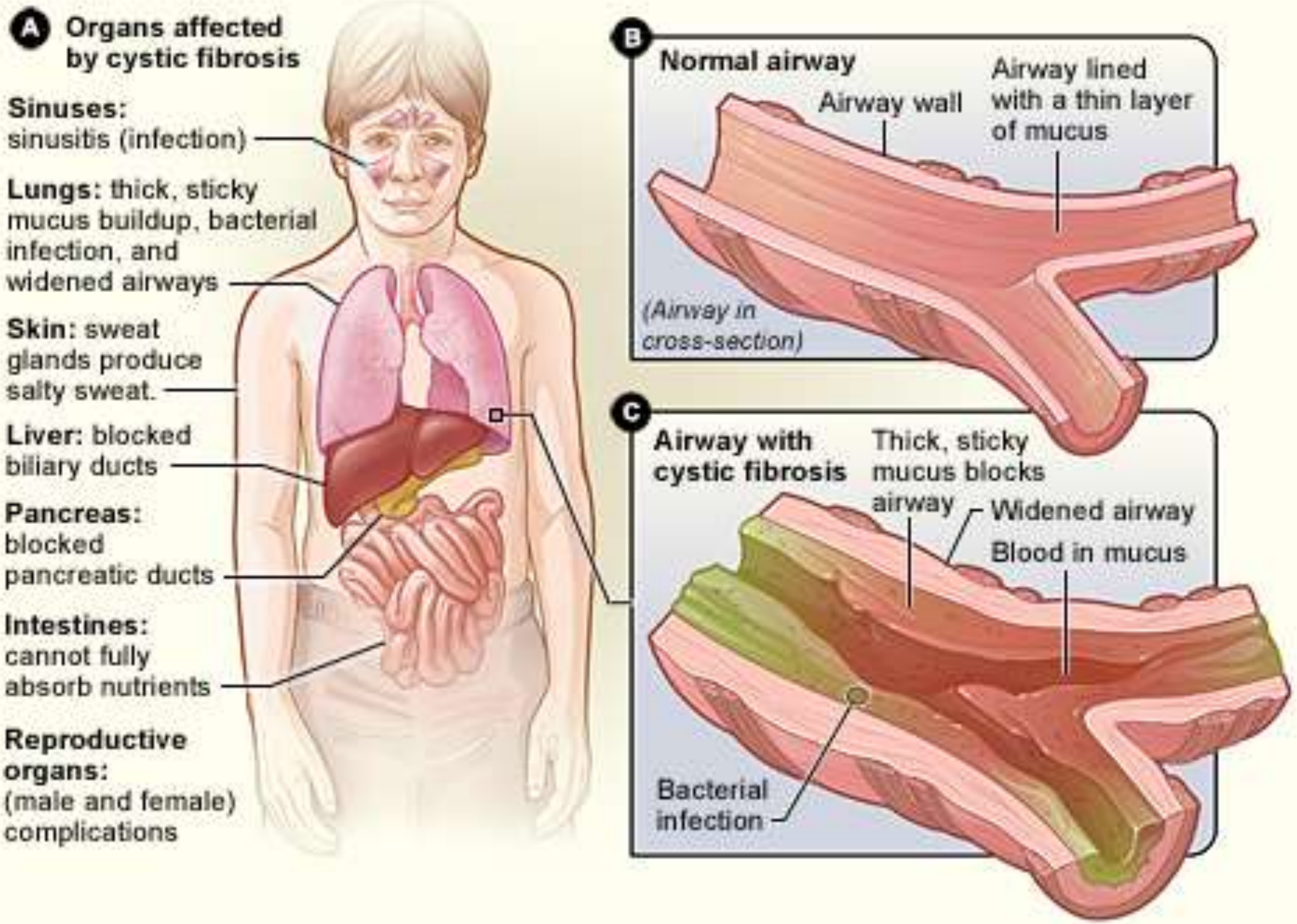
Pleiotropy

- 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 and sickle-cell disease

CFTR gene is a recessive gene
↓
when both alleles are mutated
↓
transport of Cl^- ion channels across the cell membrane is affected
↓
Cl^- will build up outside the cell
↓
↑ mucus build-up in respiratory airways & body cavities.

- → bacterial infections & blocked airway
- → Skin: sweat glands produce salty sweat
- → liver: bile duct is blocked by mucus
- → pancreas: pancreatic duct is blocked
- → intestines: inability to absorb nutrients due to mucus build-up
- → male & female sexual complications

* Respiratory, digestive, dermatological, & reproductive systems are ALL impacted by a single mutation.



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

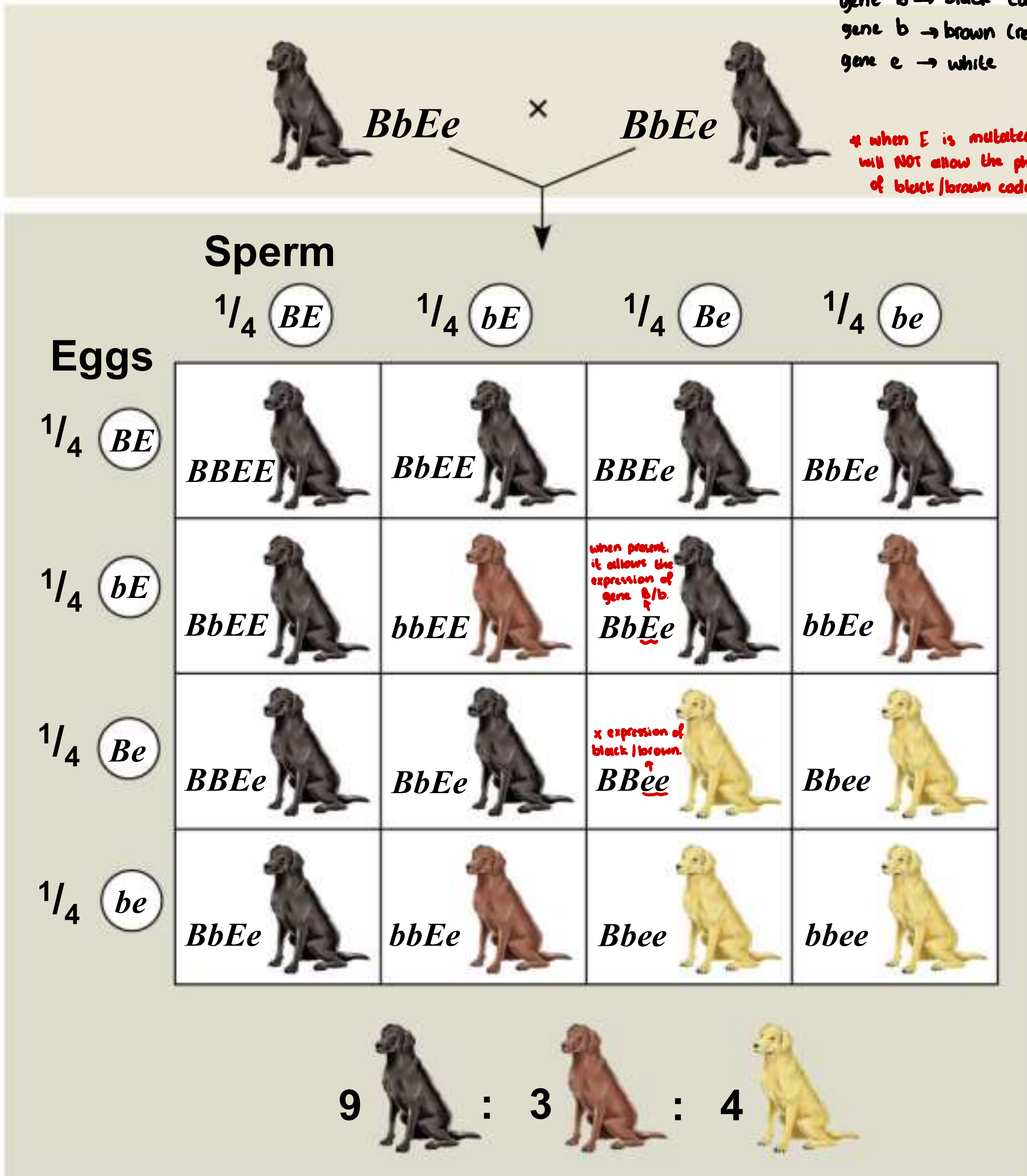
Epistasis

- 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

gene B → black (dominant)
gene b → brown (recessive)
gene e → white

* when E is mutated it will NOT allow the phenotype of black/brown code color → "E/e" has an epistatic effect on B/b.



Polygenic Inheritance

Pleiotropy vs polygenic inheritance

1 gene causes multiple phenotypic effects.

multiple genes cause 1 phenotypic effect

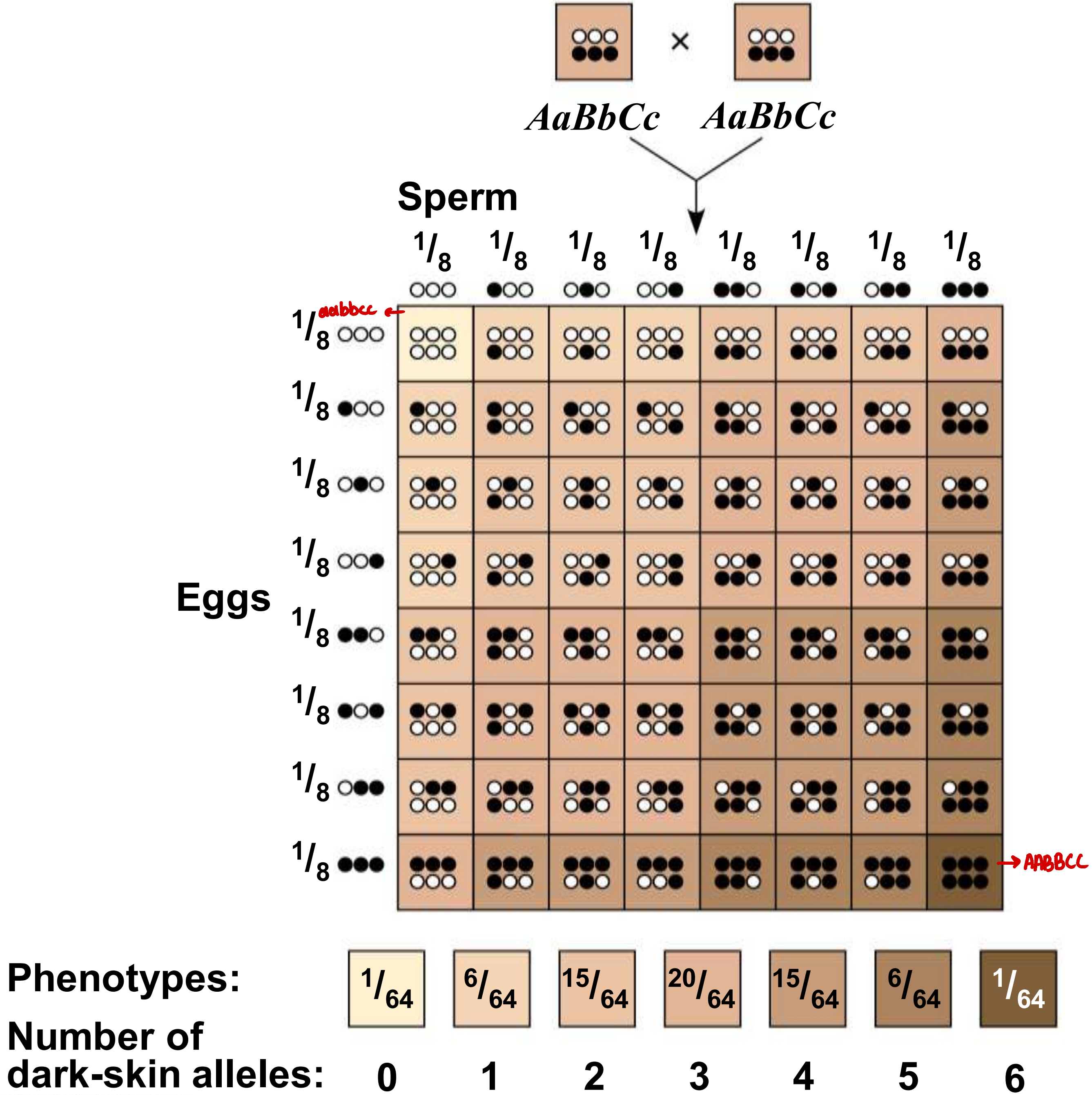
- **Quantitative characters** are those that vary in the population along a continuum
- Quantitative variation usually indicates **polygenic inheritance**, an additive effect of two or more genes on a single phenotype
- Skin color in humans is an example of polygenic inheritance

* Diseases with polygenic inheritance:

diabetes, cancer, HTN, many psychiatric diseases.

(most genetic diseases are polygenic)

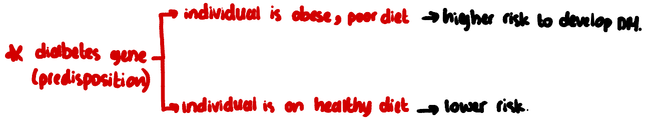
Figure 14.13


AaBbCc
AaBbCc
Sperm
Eggs
1/8
aabbcc
AABBCC
Phenotypes:
1/64
6/64
15/64
20/64
15/64
6/64
1/64
Number of dark-skin alleles:
0
1
2
3
4
5
6

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



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