PowerPoint Presentation Materials
to accompany

Genetics: Analysis and Principles

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CHAPTER 2

MENDELIAN INHERITANCE

INTRODUCTION

- Many theories of inheritance have been proposed to explain transmission of hereditary traits
  - Theory of Pangenesis
  - Theory of Preformationism
  - Blending Theory of Inheritance

INTRODUCTION

- Theory of pangenesis
  - Proposed by Hippocrates (ca. 400 B.C.)
  - “Seeds” are produced by all parts of the body
    - Collected in the reproductive organs
    - Then transmitted to offspring at moment of conception

INTRODUCTION

- Theory of preformationism
  - The organism is contained in one of the sex cells as a fully developed *homunculus*
    - Miniature human
  - With proper nourishment the *homunculus* unfolds into its adult proportions
    - The Spermists believed the *homunculus* was found in the sperm
    - The Ovists believed the *homunculus* resided in the egg

INTRODUCTION

- Blending theory of inheritance
  - Factors that control hereditary traits are maleable
  - They can blend together generation after generation

INTRODUCTION

- Gregor Mendel's pioneering experiments with garden peas refuted all of the above!

2.1 MENDEL'S LAWS OF INHERITANCE

- Gregor Johann Mendel (1822-1884) is considered the father of genetics
- His success can be attributed, in part, to
  - His boyhood experience in grafting trees
    - This taught him the importance of precision and attention to detail
  - His university experience in physics and natural history
    - This taught him to view the world as an orderly place governed by natural laws
      - These laws can be stated mathematically

2.1 MENDEL'S LAWS OF INHERITANCE

- Mendel was an Austrian monk
- He conducted his landmark studies in a small 115- by 23-foot plot in the garden of his monastery
- From 1856-1864, he performed thousands of crosses
- He kept meticulously accurate records that included quantitative analysis

2.1 MENDEL'S LAWS OF INHERITANCE

- His work, entitled "Experiments on Plant Hybrids" was published in 1866
- It was ignored for 34 years
- Probably because
  - It was published in an obscure journal
  - Lack of understanding of chromosome transmission

2.1 MENDEL'S LAWS OF INHERITANCE

- In 1900, Mendel's work was rediscovered by three botanists working independently
  - Hugo de Vries of Holland
  - Carl Correns of Germany
  - Erich von Tschermak of Austria

Mendel Chose Pea Plants as His Experimental Organism

- Hybridization
  - The mating or crossing between two individuals that have different characteristics
    - Purple-flowered plant X white-flowered plant
- Hybrids
  - The offspring that result from such a mating

Mendel Chose Pea Plants as His Experimental Organism

- Mendel chose the garden pea (*Pisum sativum)* to study the natural laws governing plants hybrids
- The garden pea was advantageous because
  - 1. It existed in several varieties with distinct characteristics
  - 2. Its structure allowed for easy crosses

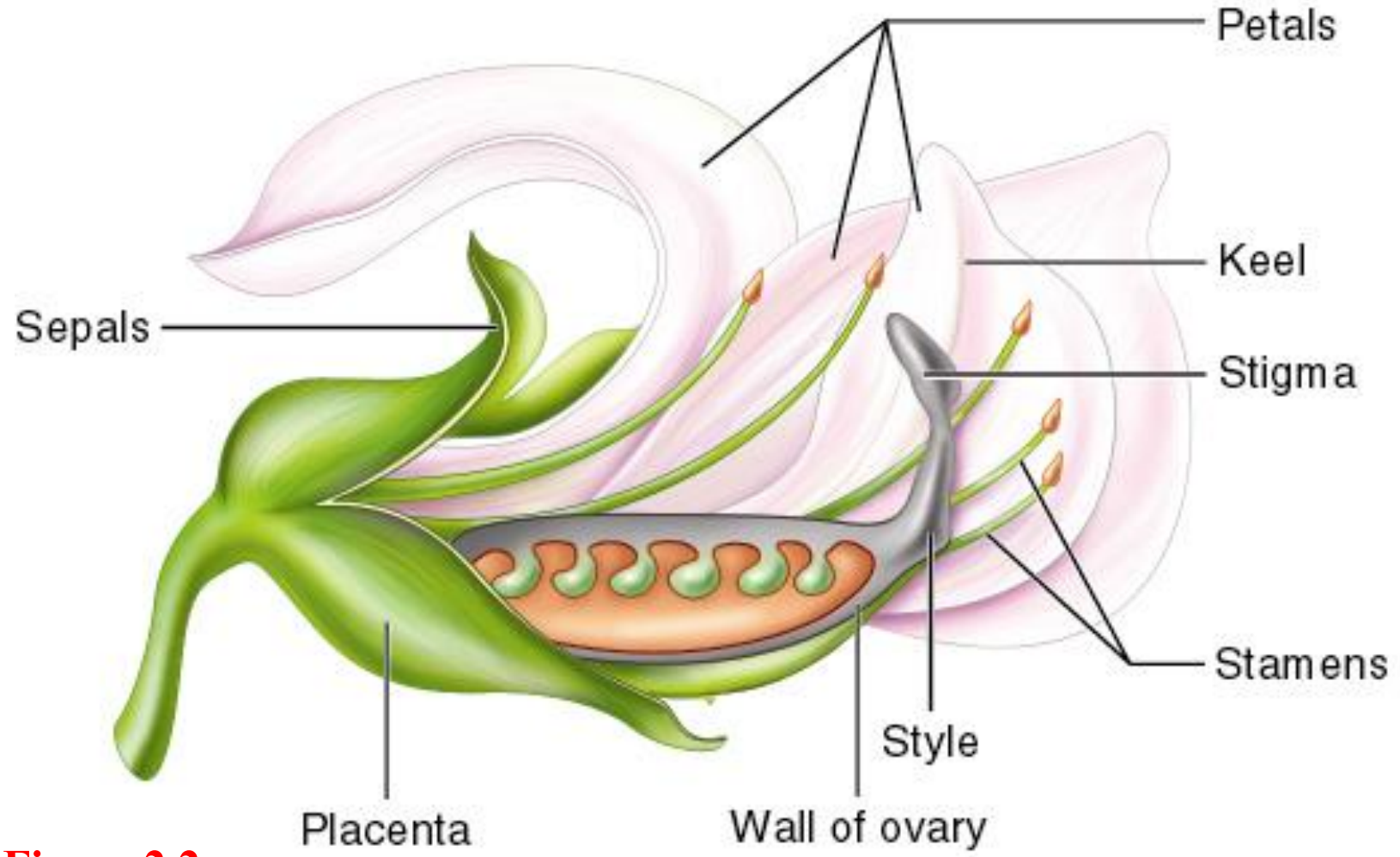
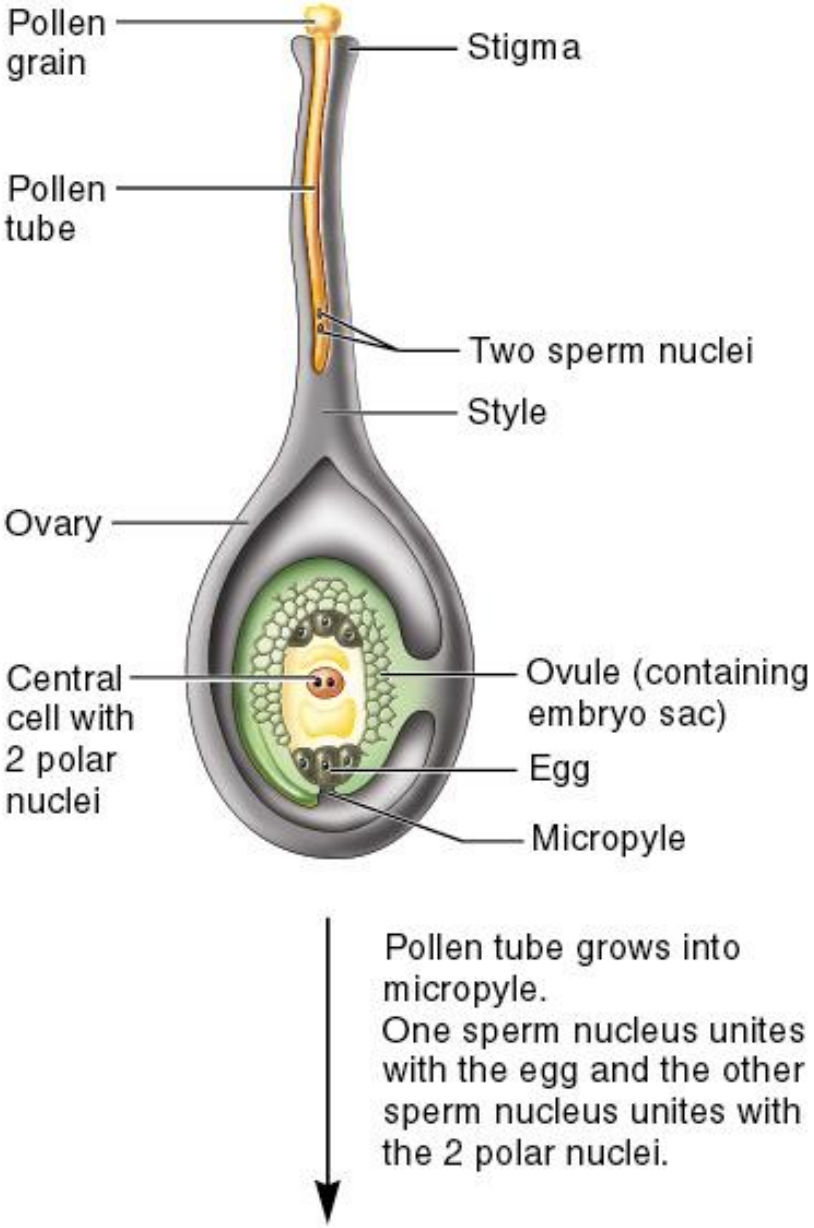
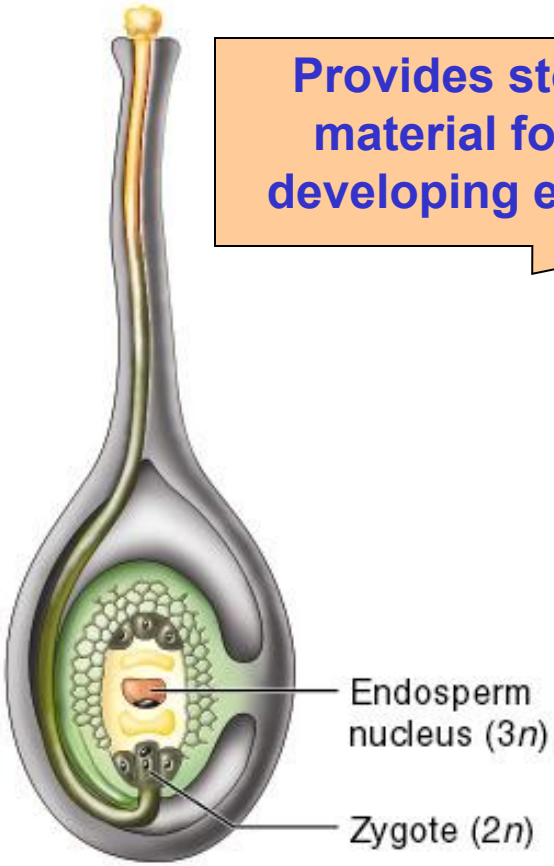


Figure 2.2

(a) Structure of a pea flower

Contain the pollen grains, where the male gametes are produced





Provides storage material for the developing embryo

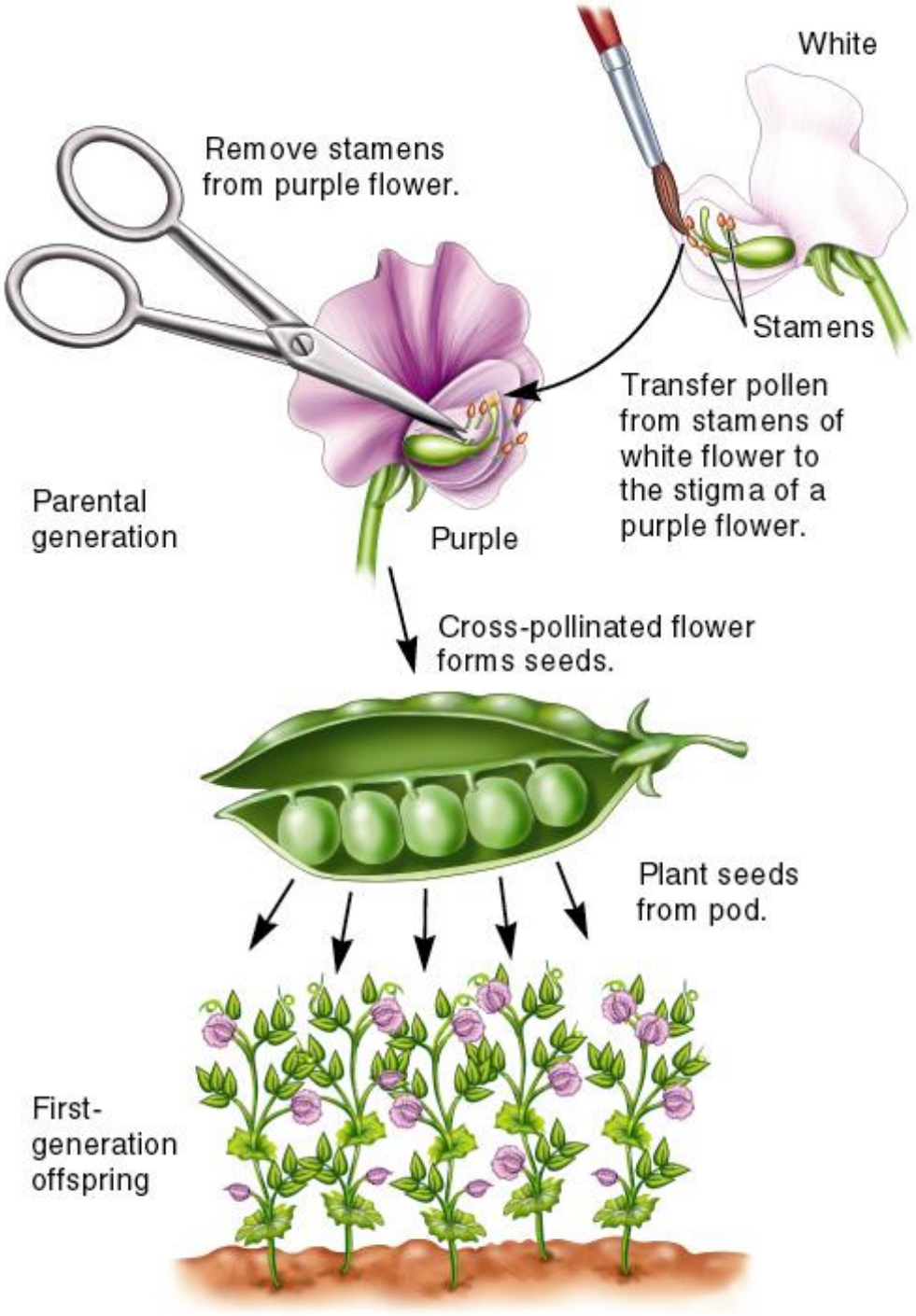
Figure 2.2

(c) Pollination and fertilization in angiosperms

Mendel Chose Pea Plants as His Experimental Organism

- Mendel carried out two types of crosses
  - 1. Self-fertilization
    - Pollen and egg are derived from the same plant
  - 2. Cross-fertilization
    - Pollen and egg are derived from different plants
    - Refer to Figure 2.3

Figure 2.3


White
Remove stamens from purple flower.
Stamens
Transfer pollen from stamens of white flower to the stigma of a purple flower.
Parental generation
Purple
Cross-pollinated flower forms seeds.
Plant seeds from pod.
First-generation offspring

Mendel Studied Seven Traits That Bred True

- The morphological characteristics of an organism are termed characters or traits
- A variety that produces the same trait over and over again is termed a true-breeder
- The seven traits that Mendel studied are illustrated in Figure 2.4

Mendel's peas

Mendel looked at seven traits or characteristics of pea plants:

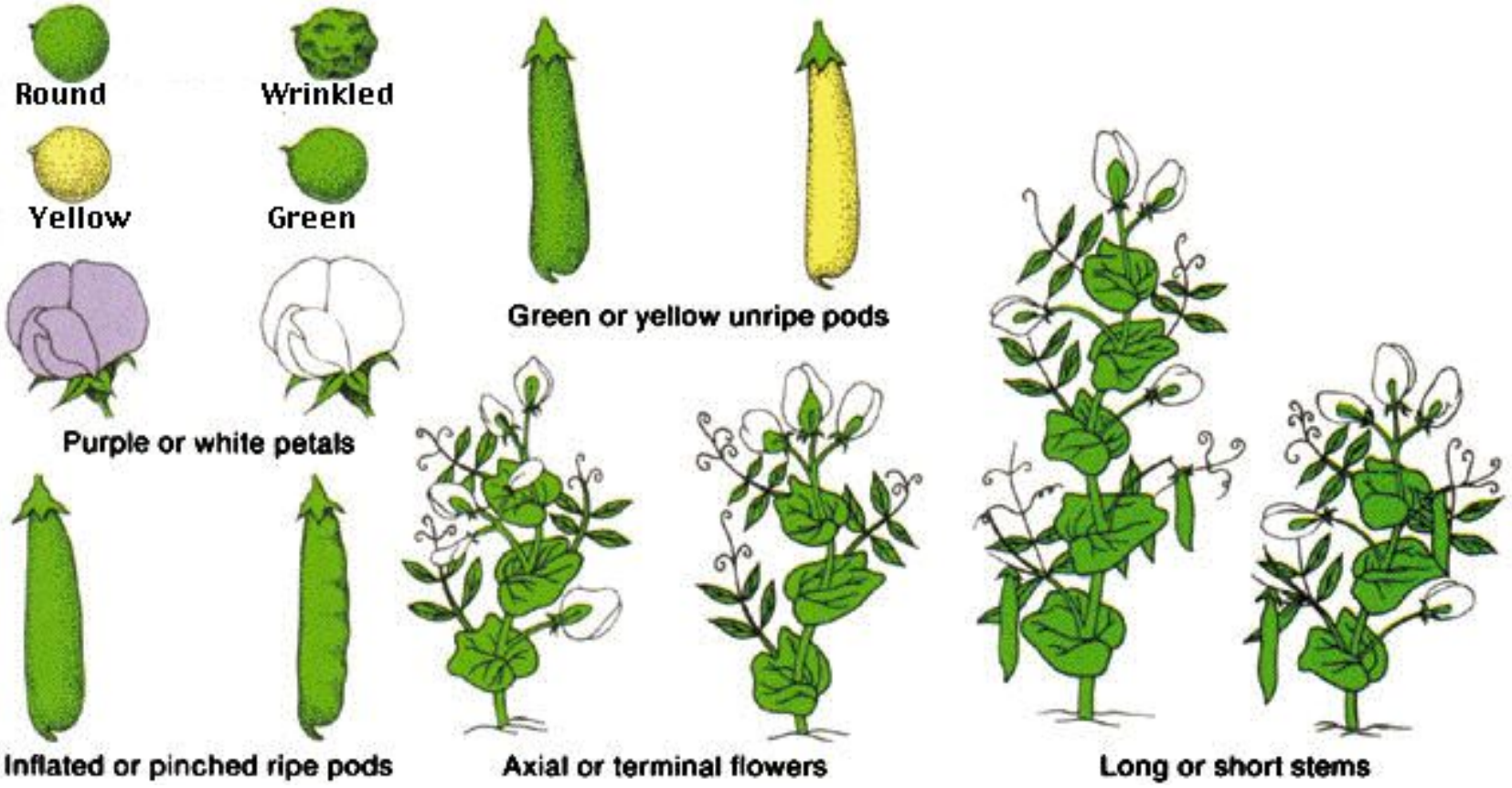
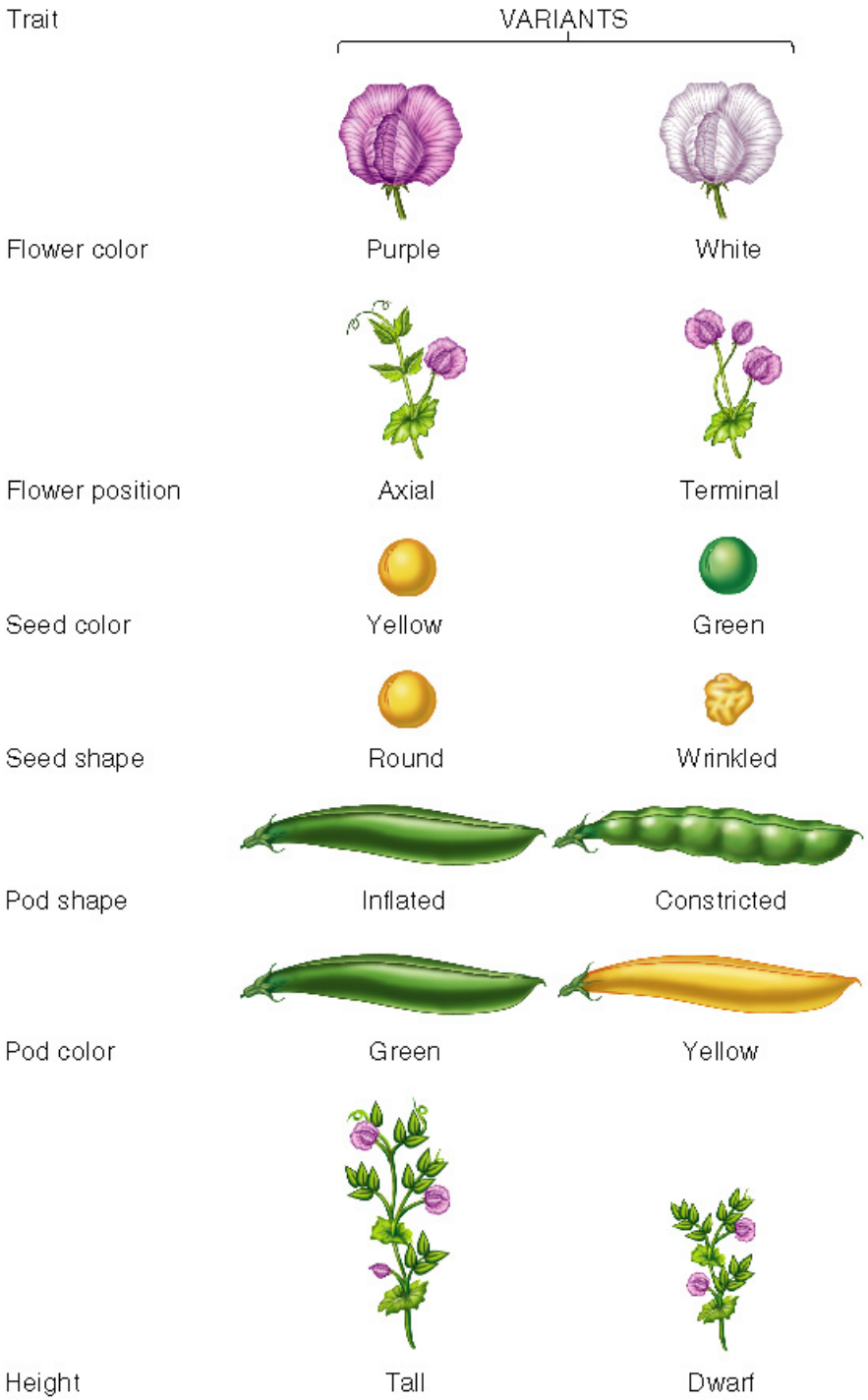


Figure 2.4


Trait
VARIANTS
Flower color
Purple
White
Flower position
Axial
Terminal
Seed color
Yellow
Green
Seed shape
Round
Wrinkled
Pod shape
Inflated
Constricted
Pod color
Green
Yellow
Height
Tall
Dwarf

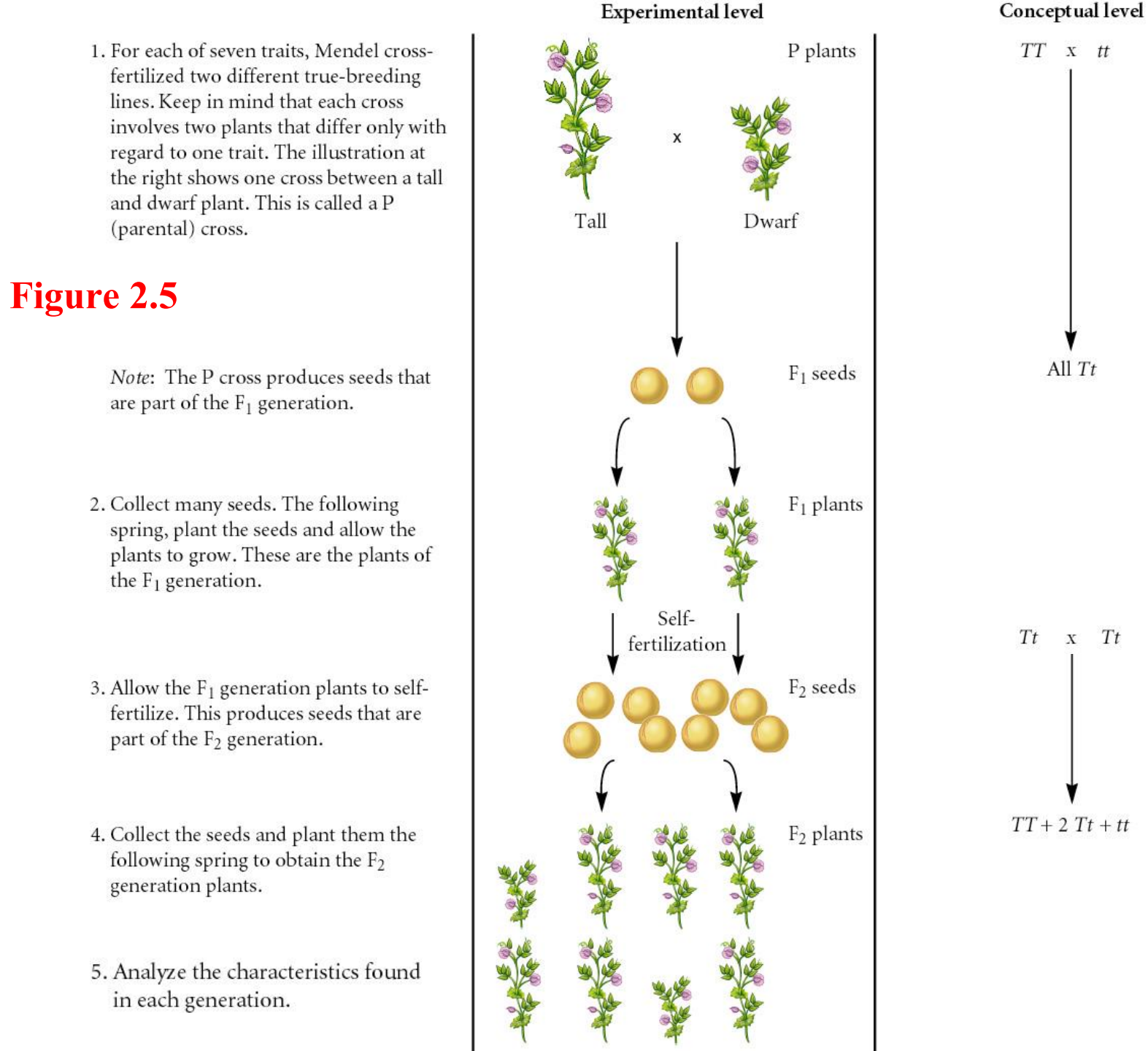
Mendel's Experiments

- Mendel did not have a hypothesis to explain the formation of hybrids
  - Rather, he believed that a quantitative analysis of crosses may provide a mathematical relationship
- Thus, he used the emperical approach
  - And tried to deduce emperical laws

Mendel's Experiments

- Mendel crossed two variants that differ in only one trait
  - This is termed a monohybrid cross
- The experimental procedure is shown in Figure 2.5

Figure 2.5


Experimental level
Conceptual level
1. For each of seven traits, Mendel cross-fertilized two different true-breeding lines. Keep in mind that each cross involves two plants that differ only with regard to one trait. The illustration at the right shows one cross between a tall and dwarf plant. This is called a P (parental) cross.
P plants
x
Tall
Dwarf
TT x tt
All Tt
Note: The P cross produces seeds that are part of the F1 generation.
F1 seeds
2. Collect many seeds. The following spring, plant the seeds and allow the plants to grow. These are the plants of the F1 generation.
F1 plants
Self-fertilization
Tt x Tt
3. Allow the F1 generation plants to self-fertilize. This produces seeds that are part of the F2 generation.
F2 seeds
4. Collect the seeds and plant them the following spring to obtain the F2 generation plants.
F2 plants
TT + 2 Tt + tt
5. Analyze the characteristics found in each generation.

DATA FROM MONOHYBRID CROSSES

P Cross	F_1 generation	F_2 generation	Ratio
Tall X dwarf stem	All tall	787 tall, 277 dwarf	2.84:1
Round X wrinkled seeds	All round	5,474 round, 1,850 wrinkled	2.96:1
Yellow X Green seeds	All yellow	6,022 yellow, 2,001 green	3.01:1
Purple X white flowers	All purple	705 purple, 224 white	3.15:1
Axial X terminal flowers	All axial	651 axial, 207 terminal	3.14:1
Smooth X constricted pods	All smooth	882 smooth, 229 constricted	2.95:1
Green X yellow pods	All green	428 green, 152 yellow	2.82:1

Interpreting the Data

- For all seven traits studied
  - 1. The F_1 generation showed only one of the two parental traits
  - 2. The F_2 generation showed an ~ 3:1 ratio of the two parental traits

- These results refuted a blending mechanism of heredity

Interpreting the Data

- Indeed, the data suggested a particulate theory of inheritance

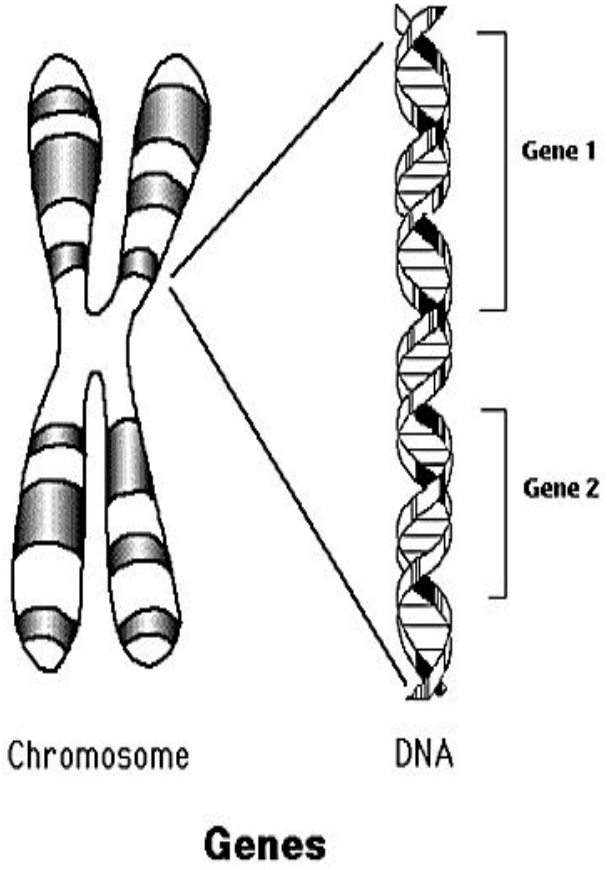
- Mendel postulated the following:

- 1. A pea plant contains two discrete hereditary factors, one from each parent
- 2. The two factors may be identical or different
- 3. When the two factors of a single trait are different
  - One is dominant and its effect can be seen
  - The other is recessive and is not expressed
- 4. During gamete formation, the paired factors segregate randomly so that half of the gametes received one factor and half of the gametes received the other
  - This is Mendel's Law of Segregation
  - Refer to Figure 2.6

- But first, let's introduce a few terms
  - Mendelian factors are now called genes
  - Alleles are different versions of the same gene
  - An individual with two identical alleles is termed homozygous
  - An individual with two different alleles, is termed heterozygous
  - Genotype refers to the specific allelic composition of an individual
  - Phenotype refers to the outward appearance of an individual

Genetic Information

- **Gene** – basic unit of genetic information. Genes determine the inherited characters.
- **Genome** – the collection of genetic information.
- **Chromosomes** – storage units of *genes*.
- **DNA** - is a nucleic acid that contains the genetic instructions specifying the biological development of all cellular forms of life

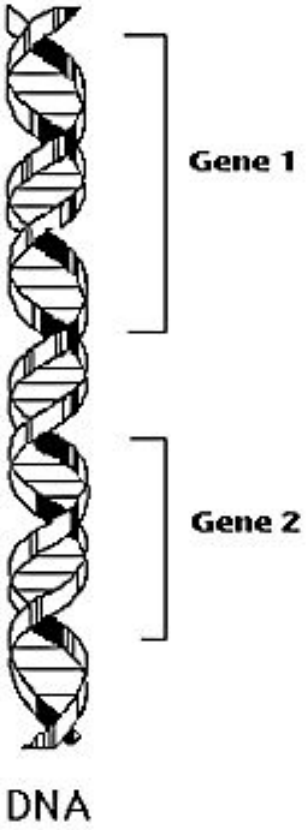


Chromosome Logical Structure

- **Locus** – location of a *gene/marker* on the chromosome.
- **Allele** – one variant form of a gene/marker at a particular *locus*.

Locus1
Possible Alleles: A1,A2

Locus2
Possible Alleles: B1,B2,B3

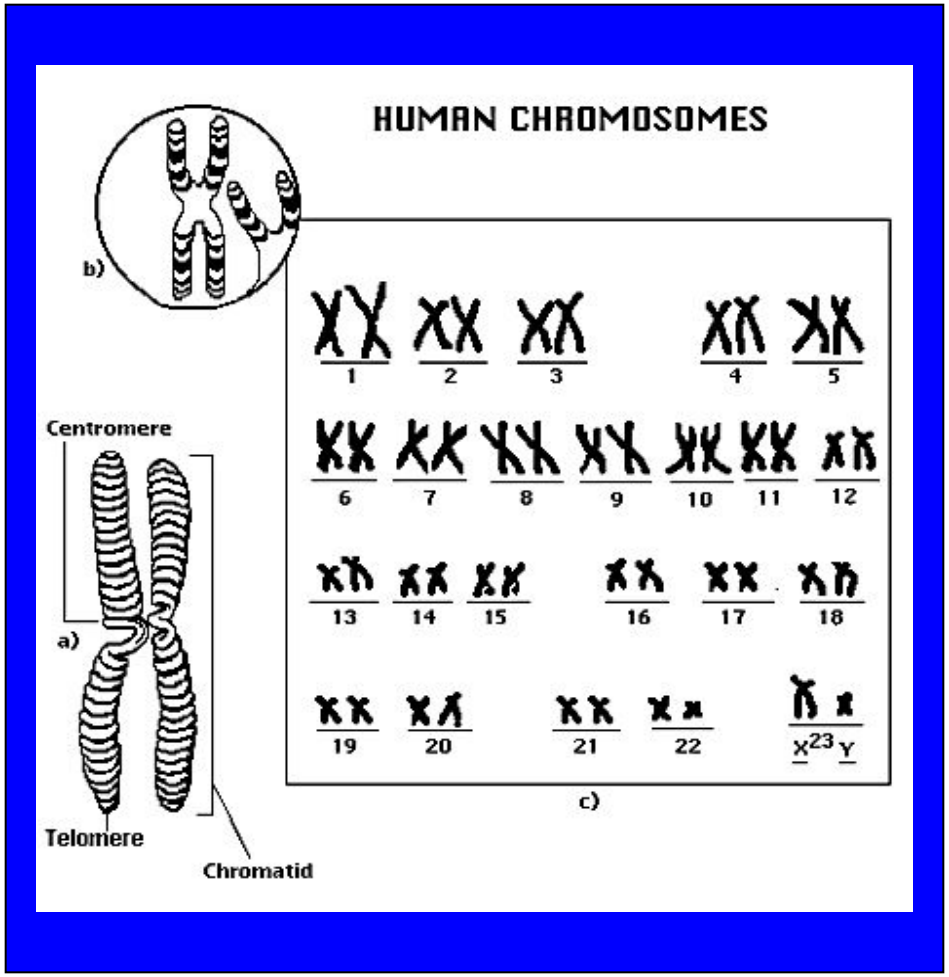


Human Genome

Most human cells contain 46 chromosomes:

- 2 **sex chromosomes** (X,Y):
  XY – in males.
  XX – in females.

- 22 pairs of chromosomes named **autosomes**.

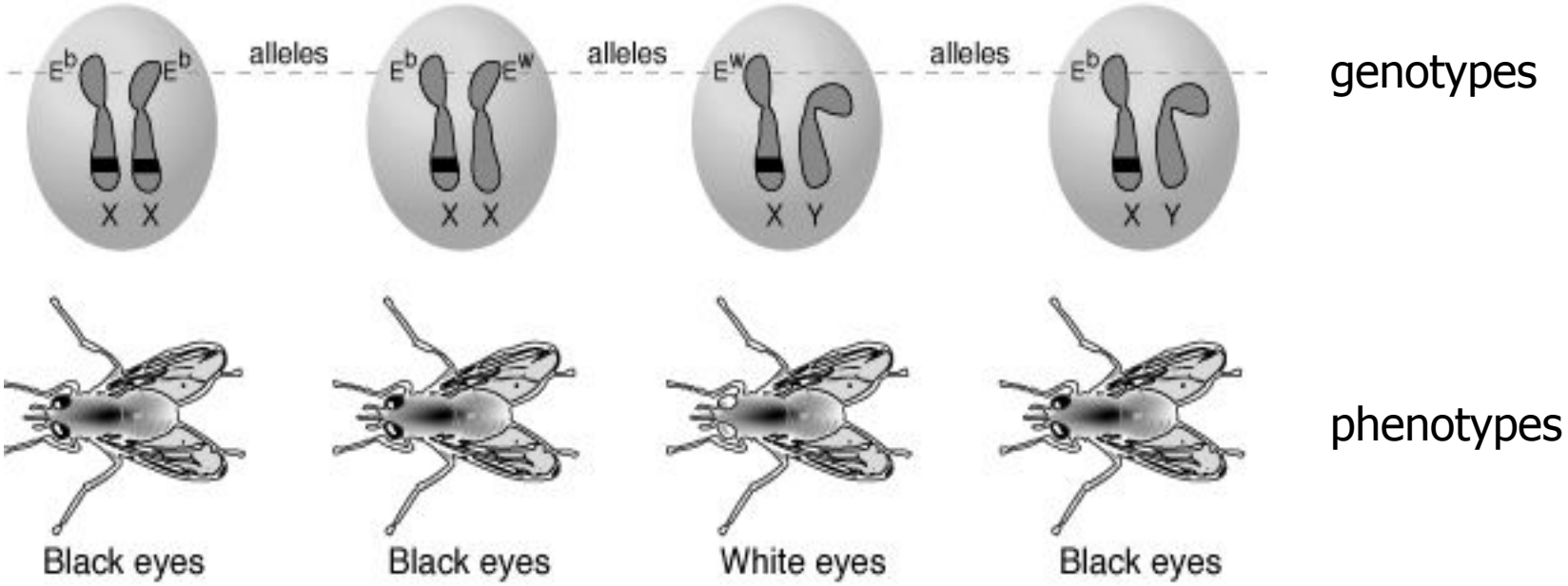


Genotypes ⟺ Phenotypes

- At each locus (except for sex chromosomes) there are 2 genes. These constitute the individual's ***genotype*** at the locus.

- The expression of a genotype is termed a ***phenotype***. For example, hair color, weight, or the presence or absence of a disease.

Genotypes ⟷ Phenotypes (example)

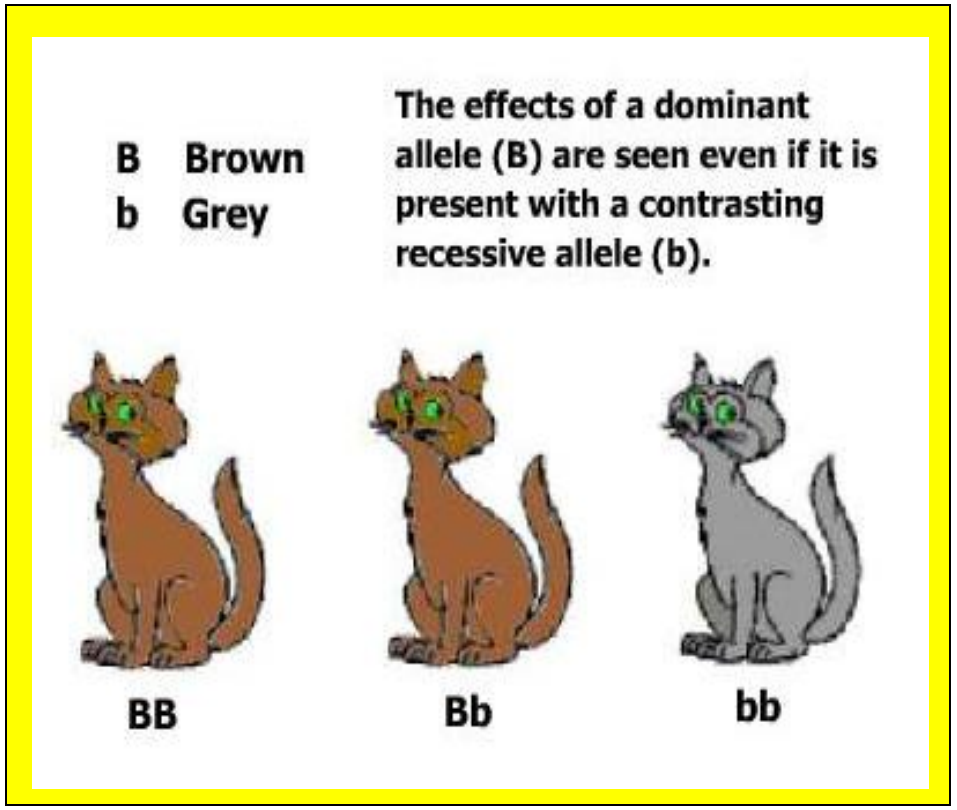


- E^b- ***dominant*** allele.
- E^w- ***recessive*** allele.

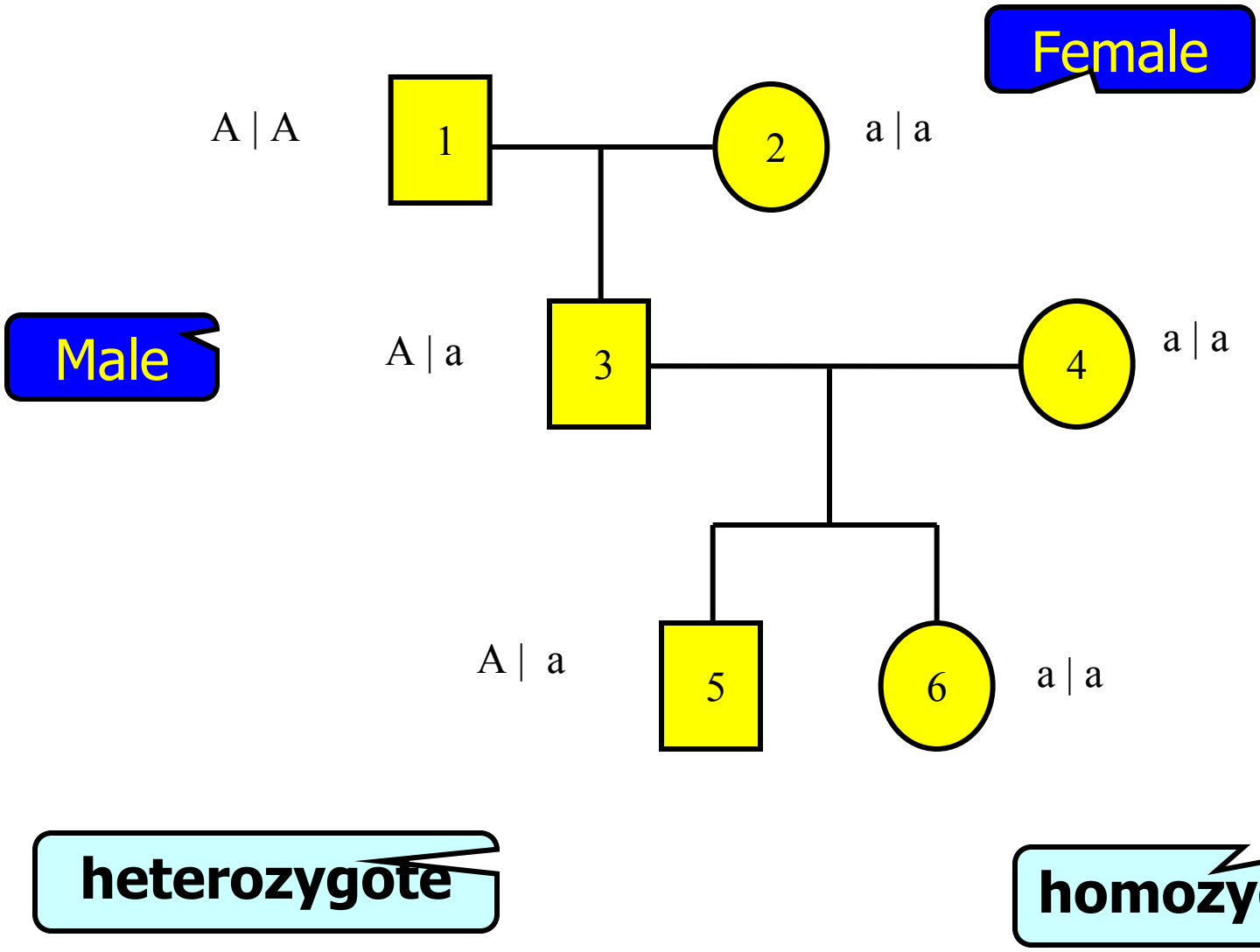
Dominant vs. Recessive

A ***dominant*** allele is expressed even if it is paired with a recessive allele.

A ***recessive*** allele is only visible when paired with another recessive allele.

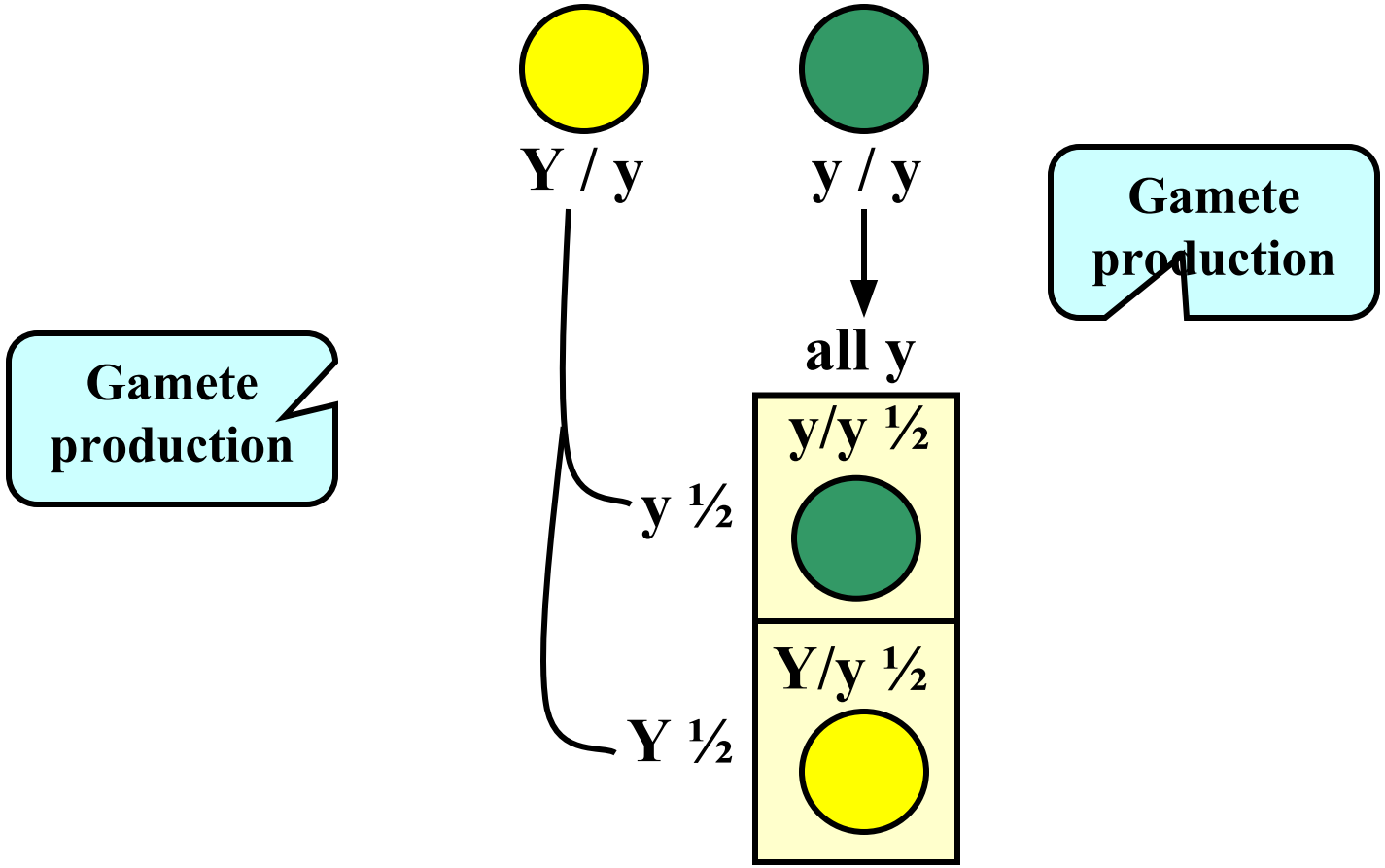


One Locus Inheritance



Mendel's 1st Law

Two members of a gene pair segregate from each other into the gametes, so half the gametes carry one member of the pair and the other half carry the other member of the pair.



Calculating Probabilities

- We want to predict patterns of inheritance of traits and diseases in pedigrees.
- E.g., we want to know the likelihood that a person chosen at random from the study population will have blue eyes.

10

blue eyed

20

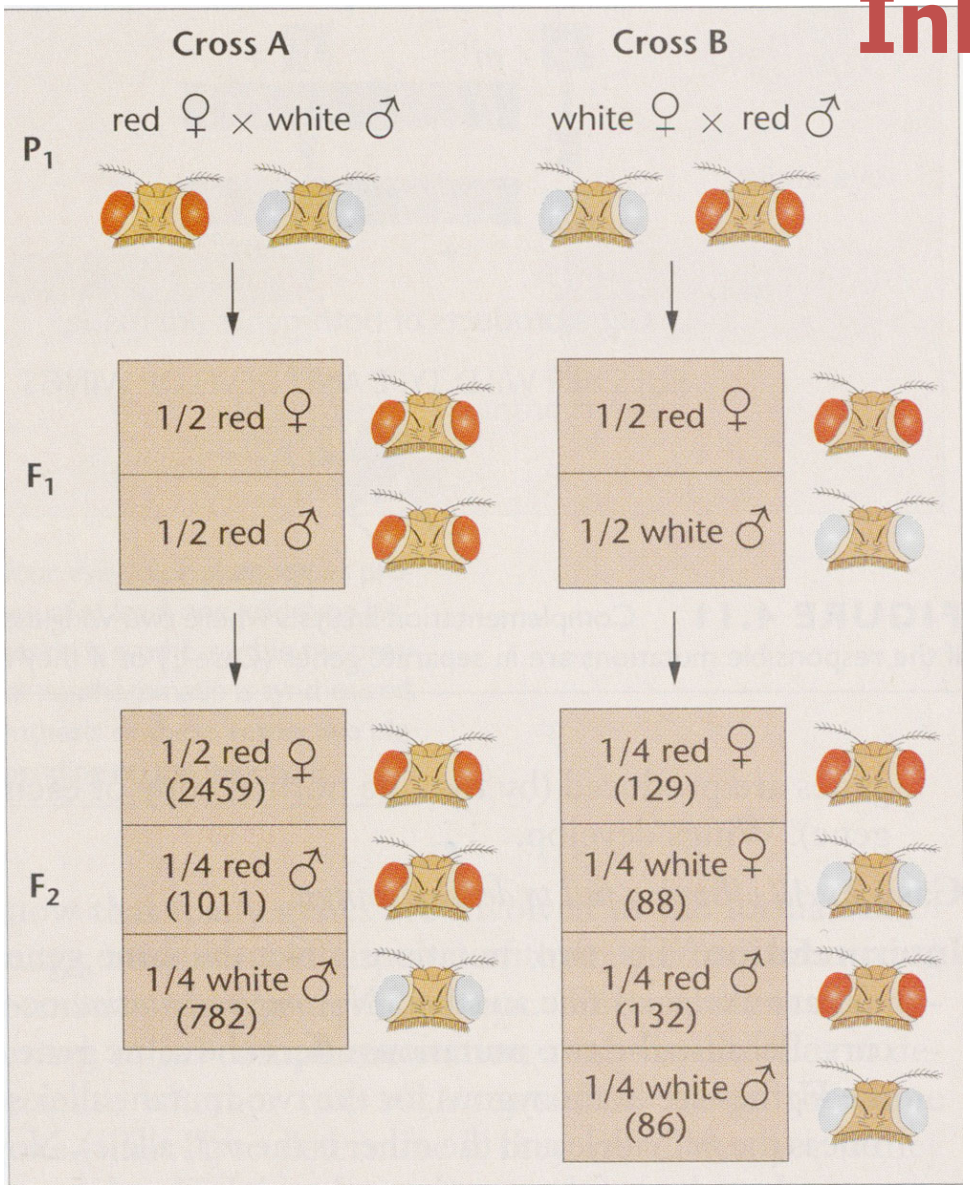
brown eyed

$$P(\text{blue eyed}) = \frac{10}{30}$$

$$P(\text{brown eyed}) = \frac{20}{30}$$

$$P(\text{blue eyed}) + P(\text{brown eyed}) = 1$$

X-linked Inheritance

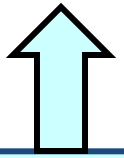


Different results obtained from reciprocal crosses between red-eyed and white-eyed Drosophila.

<u>Explanation</u>: The gene responsible for eye-color is **X-linked**. Females have X-chromosomes, while 2 males have 1 X-chromosome .and 1 Y-chromosome

Mendel's 2nd Law

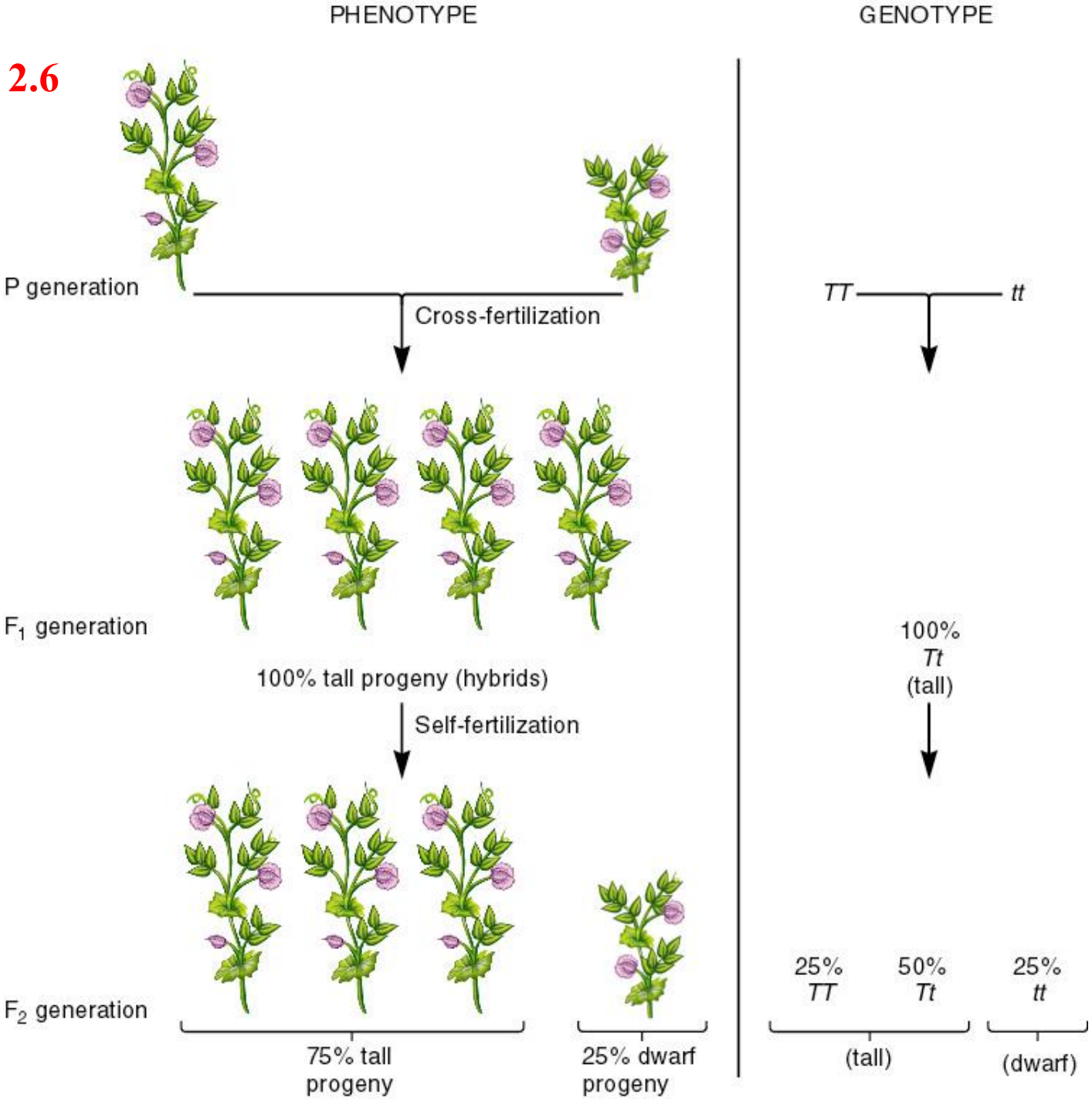
- Different gene pairs assort independently in gamete formation.



.This "law" is true only in some cases

Gene pairs on **SEPARATE CHROMOSOMES** assort independently at meiosis.

Figure 2.6


PHENOTYPE
GENOTYPE
P generation
Cross-fertilization
TT
tt
F1 generation
100% tall progeny (hybrids)
100%
Tt
(tall)
Self-fertilization
F2 generation
75% tall
progeny
25% dwarf
progeny
25%
TT
50%
Tt
25%
tt
(tall)
(dwarf)

Punnett Squares

- A Punnett square is a grid that enables one to predict the outcome of simple genetic crosses
  - It was proposed by the English geneticist, Reginald Punnett

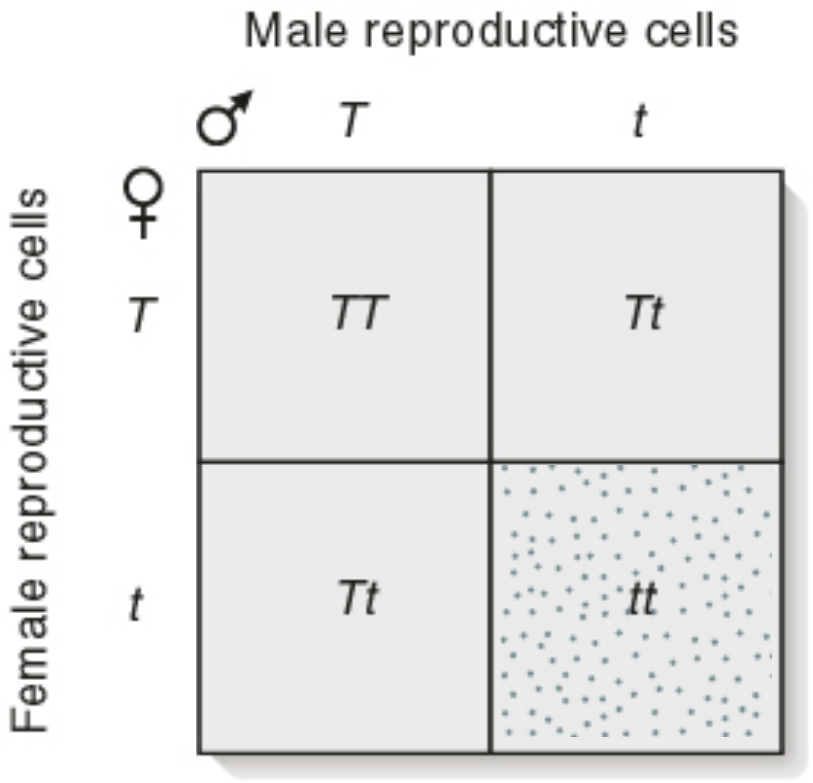
- We will illustrate the Punnett square approach using the cross of heterozygous tall plants as an example

Punnett Squares

- 1. Write down the genotypes of both parents
  - Male parent = *Tt*
  - Female parent = *Tt*

- 2. Write down the possible gametes each parent can make.
  - Male gametes: *T* or *t*
  - Female gametes: *T* or *t*

- 3. Create an empty Punnett square



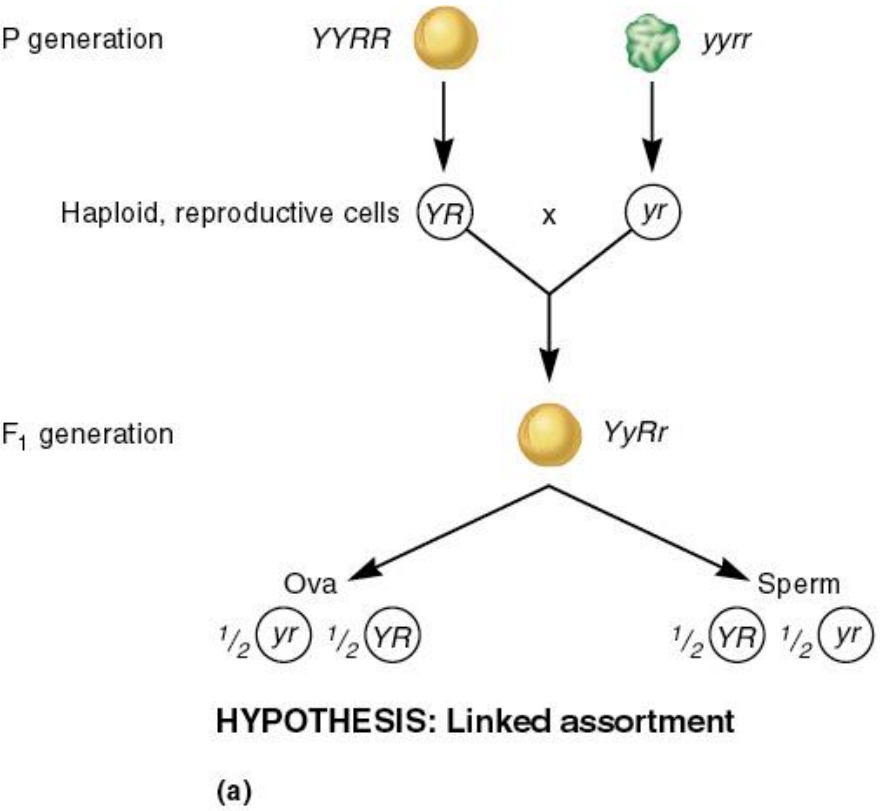
- 4. Fill in the Punnett square with the possible genotypes of the offspring

- 5. Determine the relative proportions of genotypes and phenotypes of the offspring
  - Genotypic ratio
    - TT : Tt : tt
    - 1 : 2 : 1
  - Phenotypic ratio
    - Tall : dwarf
    - 3 : 1

Mendel's Experiments

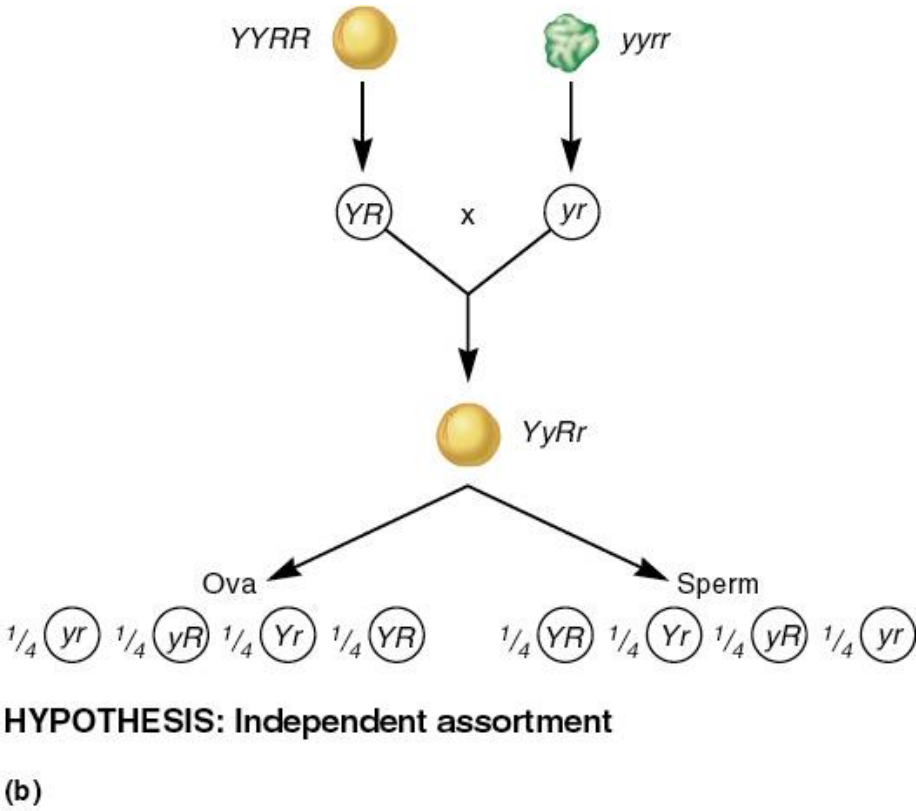
- Mendel also performed a dihybrid cross
  - Crossing individual plants that differ in two traits
- For example
  - Trait 1 = Seed texture (round vs. wrinkled)
  - Trait 2 = Seed color (yellow vs. green)
- There are two possible patterns of inheritance for these traits
  - Refer to Figure 2.7

Figure 2.7



HYPOTHESIS: Linked assortment

(a)



HYPOTHESIS: Independent assortment

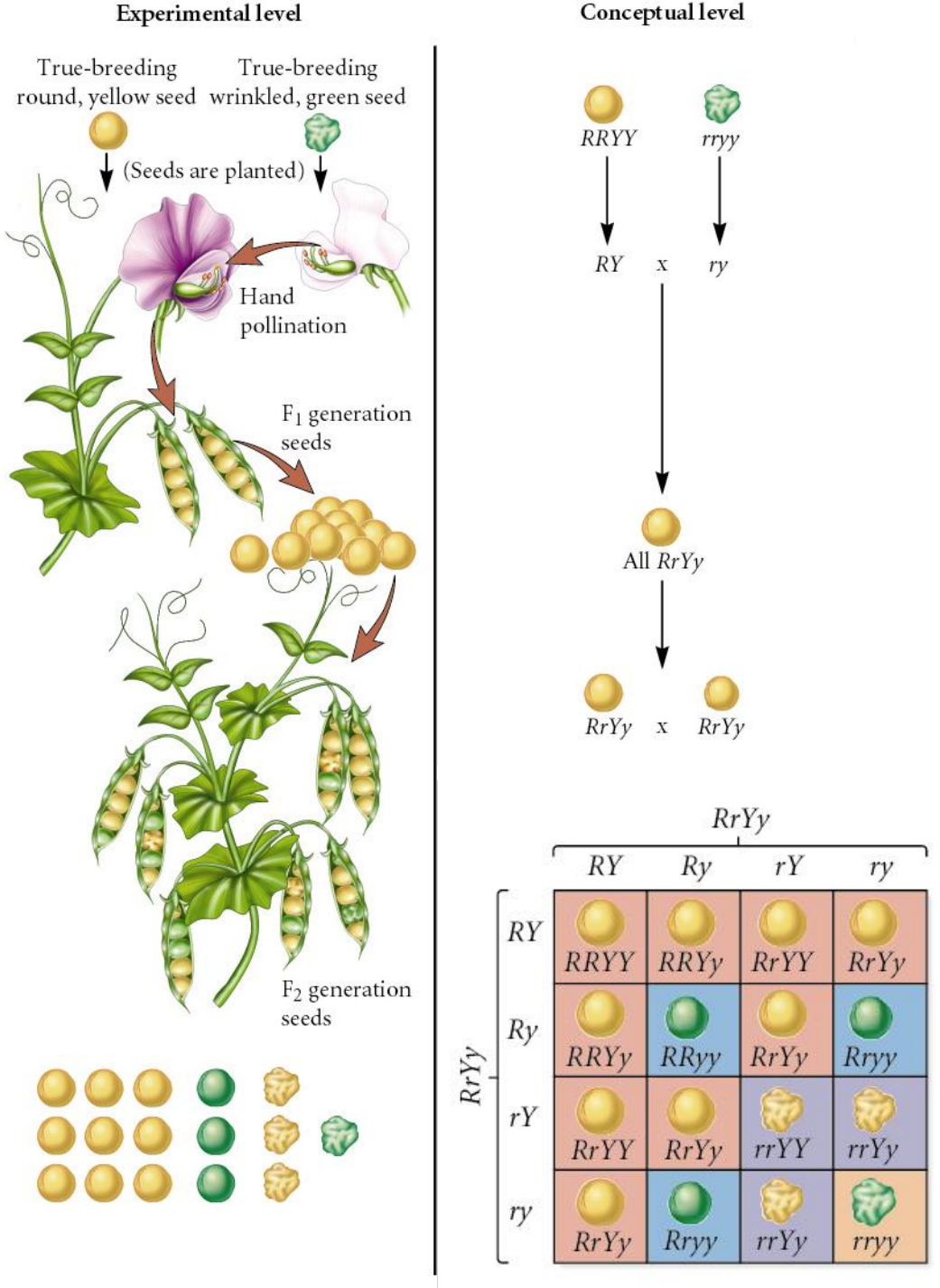
(b)

Mendel's Experiments

- The experimental procedure for the dihybrid cross is shown in Figure 2-8

Figure 2.8

1. Cross the two true-breeding plants to each other. This produces F_1 generation seeds.
2. Collect many seeds and record their phenotype.
3. F_1 seeds are planted and grown, and the F_1 plants are allowed to self-fertilize. This produces seeds that are part of the F_2 generation.
4. Analyze the characteristics found in the F_2 generation seeds.



DATA FROM DIHYBRID CROSSES

P Cross	F_1 generation	F_2 generation
Round, Yellow seeds X wrinkled, green seeds	All round, yellow	315 round, yellow seeds 101 wrinkled, yellow seeds 108 round, green seeds 32 green, wrinkled seeds

Interpreting the Data

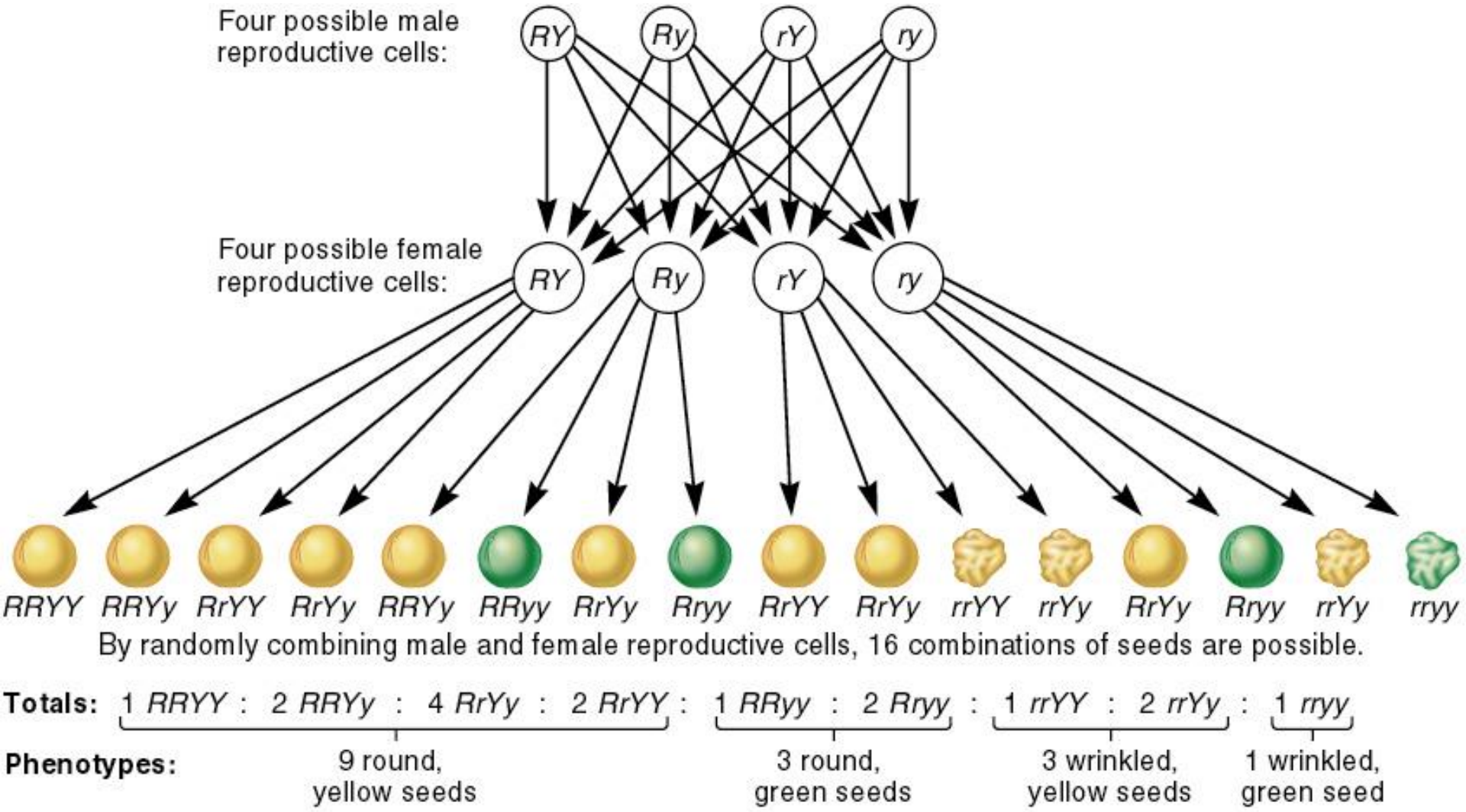
- The F_2 generation contains seeds with novel combinations (ie: not found in the parentals)
  - Round and Green
  - Wrinkled and Yellow
- These are called nonparentals
- Their occurrence contradicts the linkage model
  - Refer to Figure 2.7*a*

- If the genes, on the other hand, assort independently
  - Then the predicted phenotypic ratio in the F2 generation would be 9:3:3:1

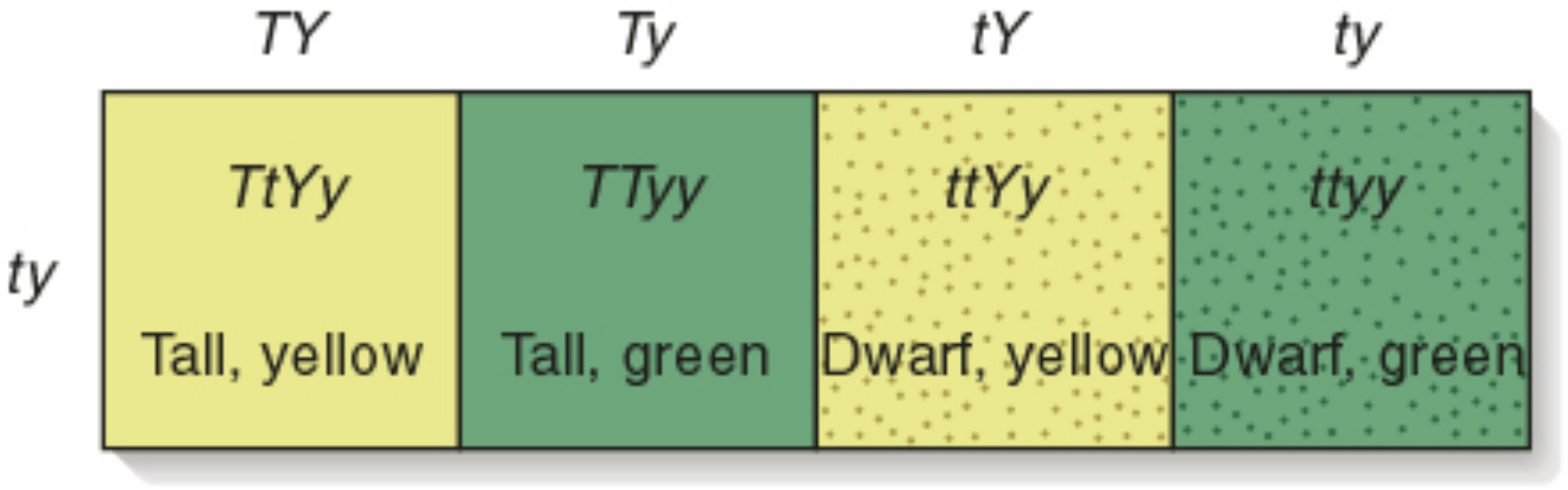
P Cross	F_1 generation	F_2 generation	Ratio
Round, Yellow seeds X wrinkled, green seeds	All round, yellow	315 round, yellow seeds	9.8
		101 wrinkled, yellow seeds	3.2
		108 round, green seeds	3.4
		32 green, wrinkled seeds	1.0

- Mendel's data was very close to segregation expectations
- Thus, he proposed the law of Independent assortment
  - During gamete formation, the segregation of any pair of hereditary determinants is independent of the segregation of other pairs

Figure 2.9



- Independent assortment is also revealed by a dihybrid test-cross
  - *TtYy* X *ttyy*



- Thus, if the genes assort independently, the expected phenotypic ratio among the offspring is 1:1:1:1

Punnett Squares

- Punnett squares can also be used to predict the outcome of crosses involving two independently assorting genes

Cross: *TtYy* x *TtYy*

♀ \ ♂	*TY*	*Ty*	*tY*	*ty*
TY	*TTYY* Tall, yellow	*TTYy* Tall, yellow	*TtYY* Tall, yellow	*TyYy* Tall, yellow
Ty	*TTYy* Tall, yellow	*TTyy* Tall, green	*TtYy* Tall, yellow	*Ttyy* Tall, green
tY	*TtYY* Tall, yellow	*TtYy* Tall, yellow	*ttYY* Dwarf, yellow	*ttYy* Dwarf, yellow
ty	*TtYy* Tall, yellow	*Ttyy* Tall, green	*ttYy* Dwarf, yellow	*ttyy* Dwarf, green

Genotype: 1 *TTYY* : 2 *TTYy* : 4 *TyYy* : 2 *TtYY* : 1 *TTyy* : 2 *Ttyy* : 1 *ttYY* : 2 *ttYy* : 1 *ttyy*

Phenotype:

- 9 tall plants with yellow seeds
- 3 tall plants with green seeds
- 3 dwarf plants with yellow seeds
- 1 dwarf plant with green seeds

Punnett Squares

- In crosses involving three or more independently assorting genes
  - Punnett square becomes too cumbersome
    - 64 squares for three genes!
- A more reasonable alternative is the forked-line method
  - Refer to solved problem S3 at the end of the chapter

Modern Genetics

- Modern geneticists are often interested in the relationship between the outcome of traits and the molecular expression of genes
- They use the following approach
  - Identify an individual with a defective copy of the gene
  - Observe how this copy will affect the phenotype of the organism

Modern Genetics

- The defective copies are termed loss-of-function alleles
- Unknowingly, Mendel had used several of these alleles in his studies on pea plants
- Loss-of-function alleles are commonly inherited in a recessive manner

Pedigree Analysis

- When studying human traits, it is not ethical to control parental crosses (as Mendel did with peas)
  - Rather, we must rely on information from family trees or pedigrees
- Pedigree analysis is used to determine the pattern of inheritance of traits in humans
- Figure 2.10 presents the symbols used in a pedigree

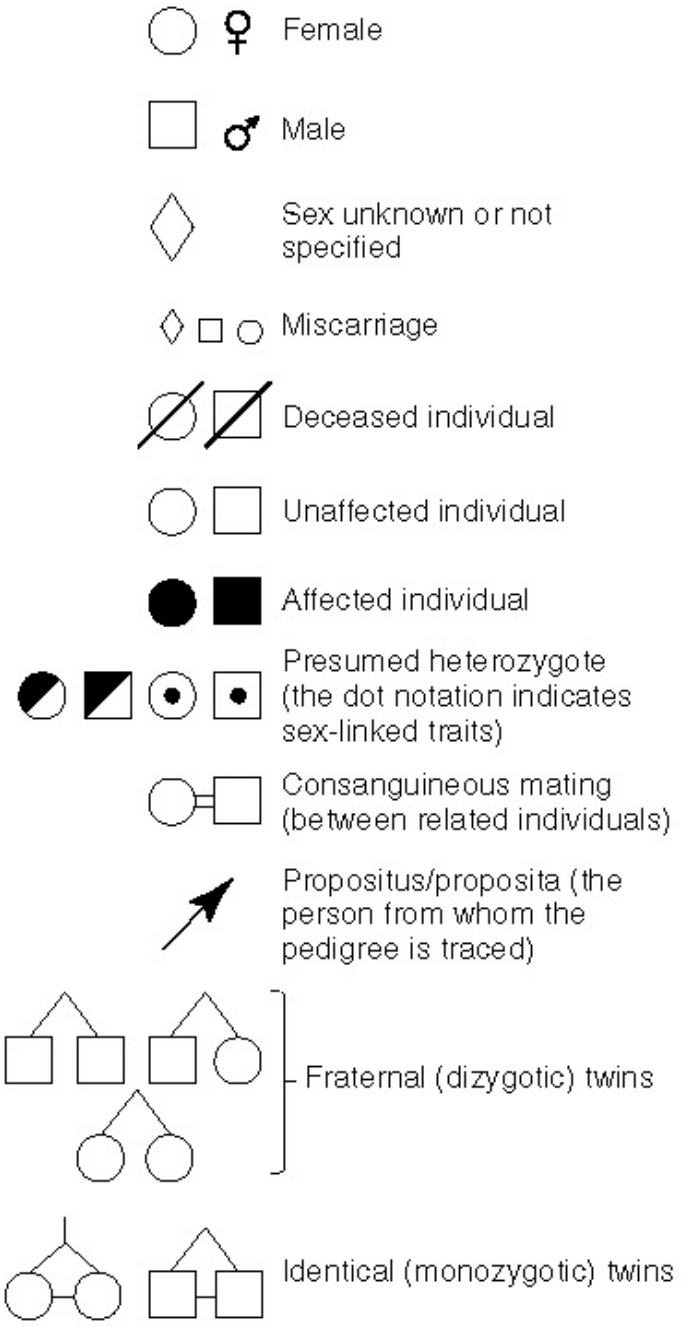


Figure 2.10 **(b)** Symbols used in a human pedigree

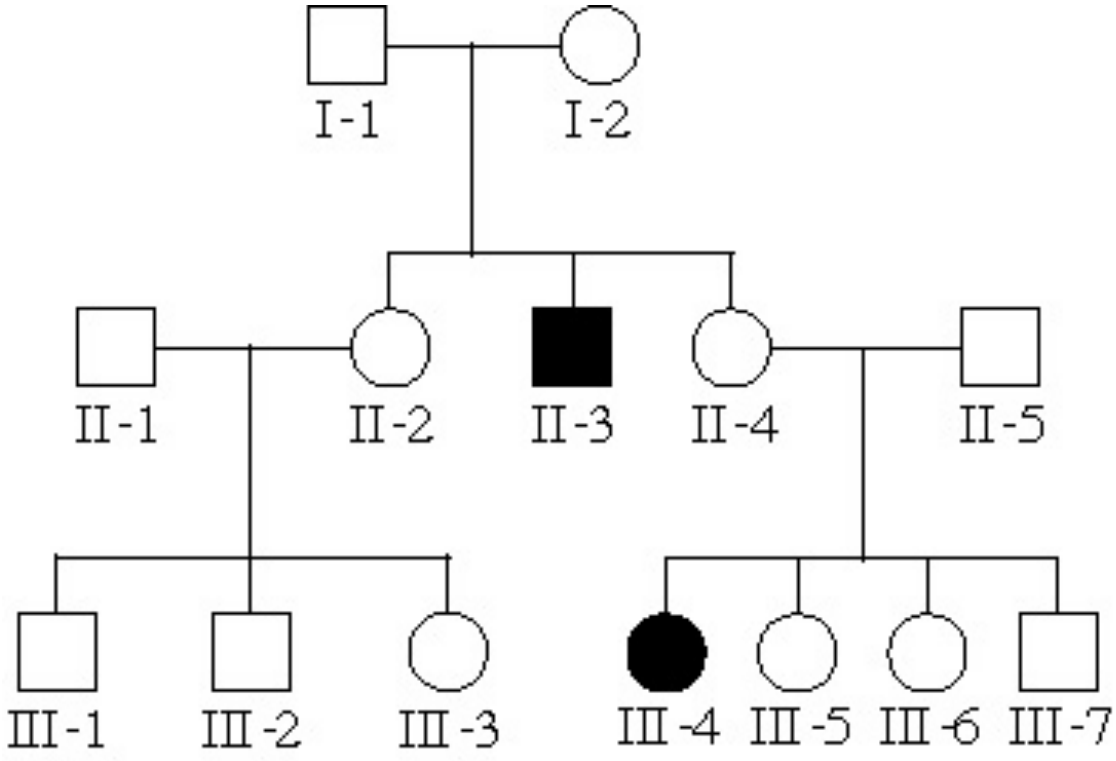


Figure 2.10 **(a)** Human pedigree showing cystic fibrosis

Pedigree Analysis

- Pedigree analysis is commonly used to determine the inheritance pattern of human genetic diseases
- Genes that play a role in disease may exist as
  - A normal allele
  - A mutant allele that causes disease symptoms
- Disease that follow a simple Mendelian pattern of inheritance can be
  - Dominant
  - Recessive

- A recessive pattern of inheritance makes two important predictions
  - 1. Two normal heterozygous individuals will have, on average, 25% of their offspring affected
  - 2. Two affected individuals will produce 100% affected offspring
- A dominant pattern of inheritance predicts that
  - An affected individual will have inherited the gene from at least one affected parent
  - Alternatively, the disease may have been the result of a new mutation that occurred during gamete formation

- Cystic fibrosis (CF)
  - A recessive disorder of humans
  - About 3% of caucasians are carriers
  - The gene encodes a protein called the cystic fibrosis transmembrane conductance regulator (CFTR)
    - The CFTR protein regulates ion transport across cell membranes
  - The mutant allele creates an altered CFTR protein that ultimately causes ion imbalance
    - This leads to abnormalities in the pancreas, skin, intestine, sweat glands and lungs

Medical Genetics

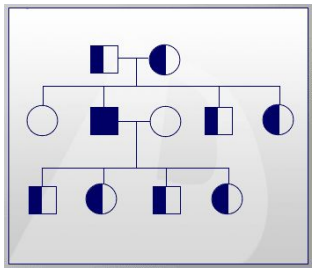
When studying rare disorders, 6 general patterns of inheritance are observed:

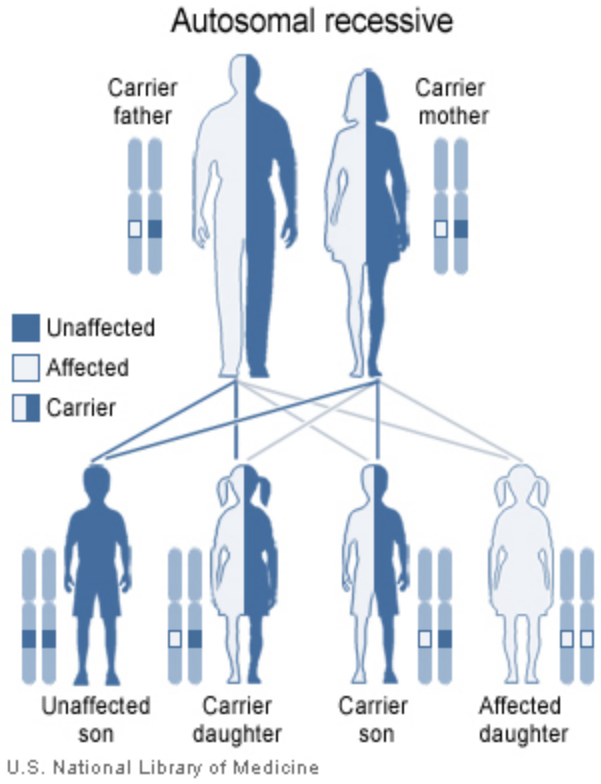
- Autosomal recessive
- Autosomal dominant
- X-linked recessive
- X-linked dominant
- Codominant
- Mitochondrial

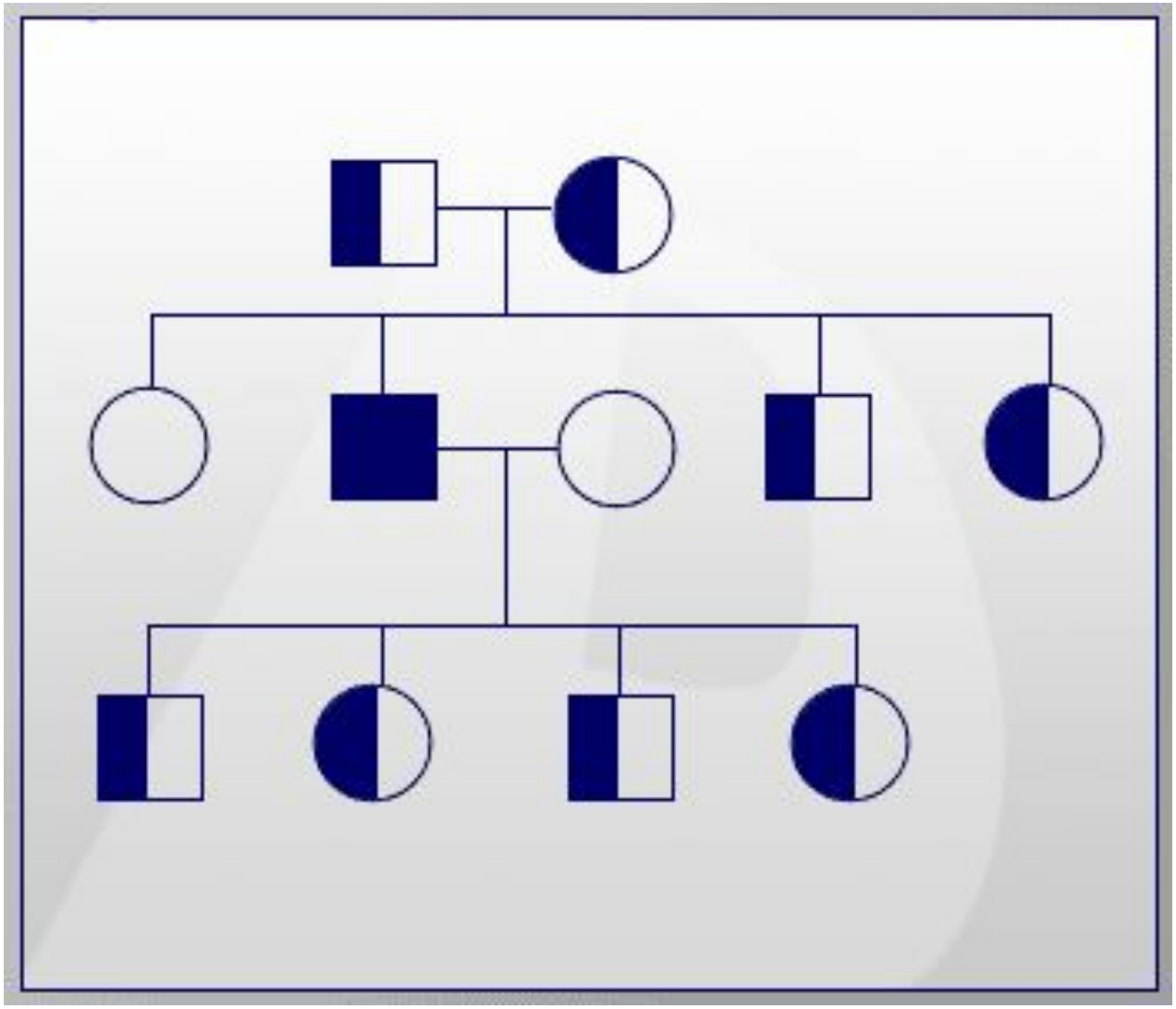
Medical Genetics (cont.)

Autosomal recessive

- The disease appears in male and female children of unaffected parents.
- e.g., cystic fibrosis



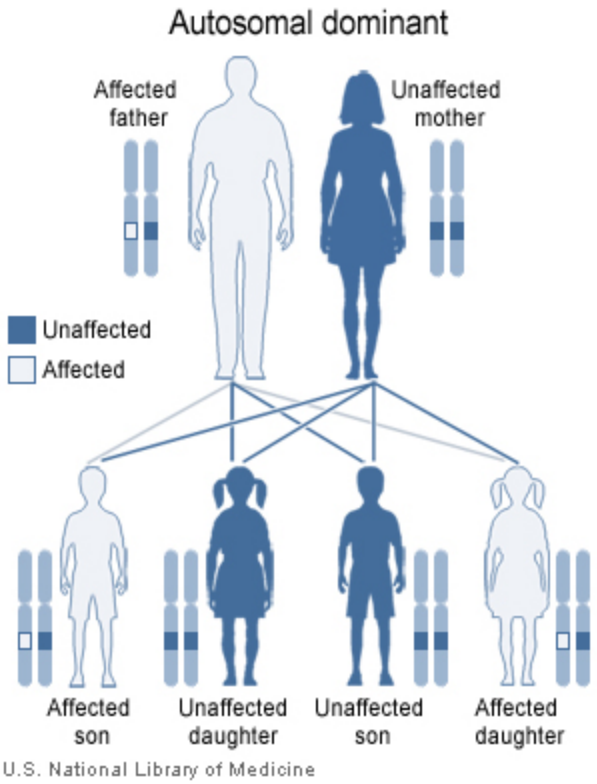


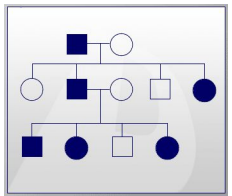


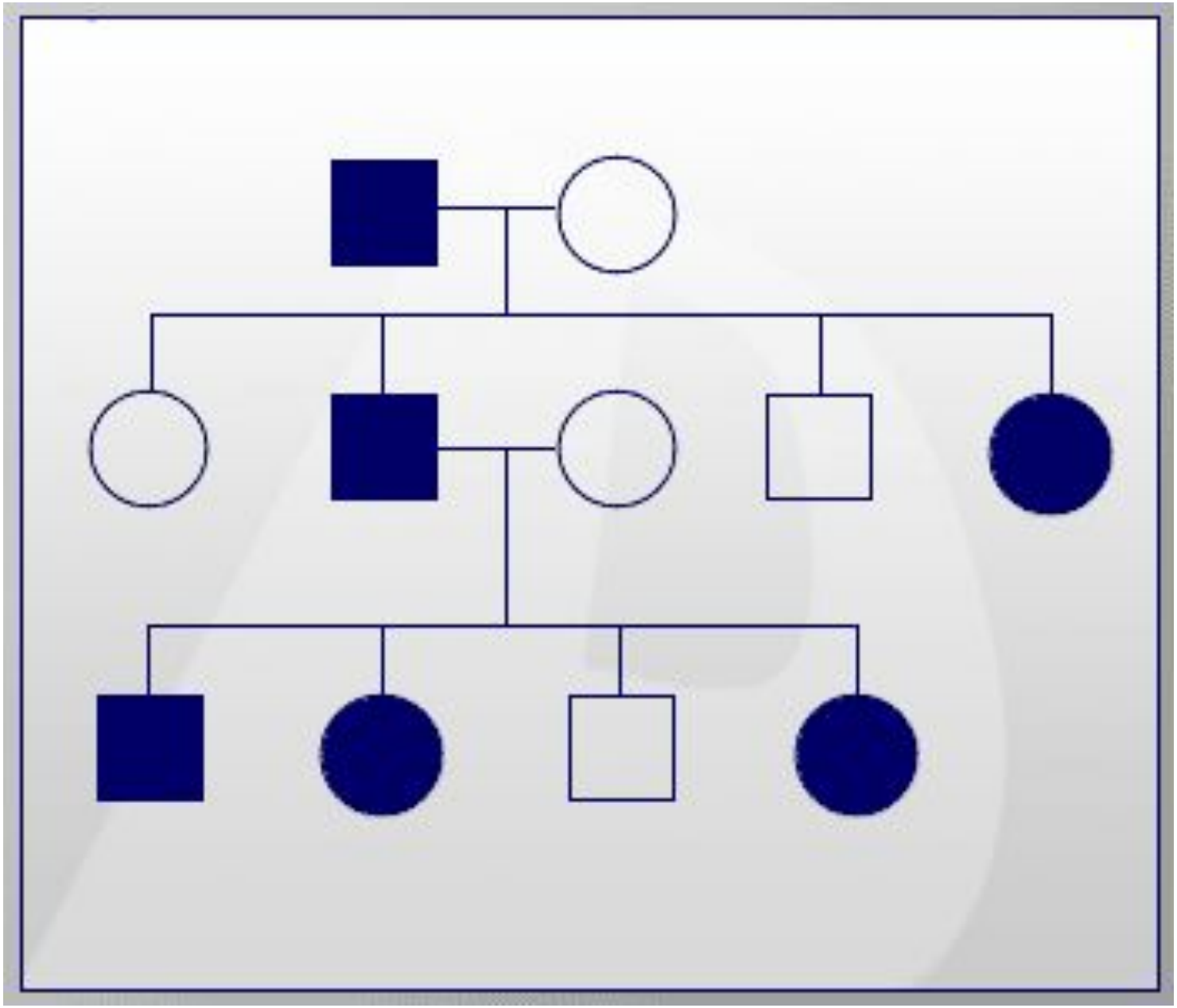
Medical Genetics (cont.)

Autosomal dominant

- Affected males and females appear in each generation of the pedigree.
- Affected mothers and fathers transmit the phenotype to both sons and daughters.
- e.g., Huntington disease.



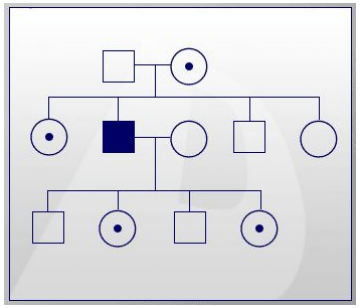


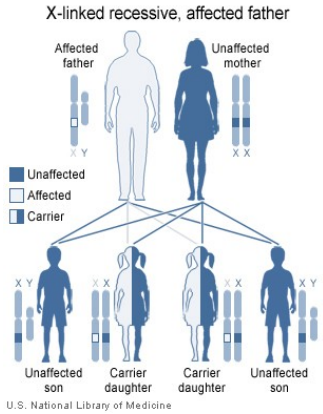


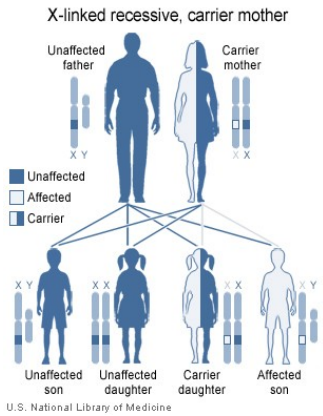
Medical Genetics (cont.)

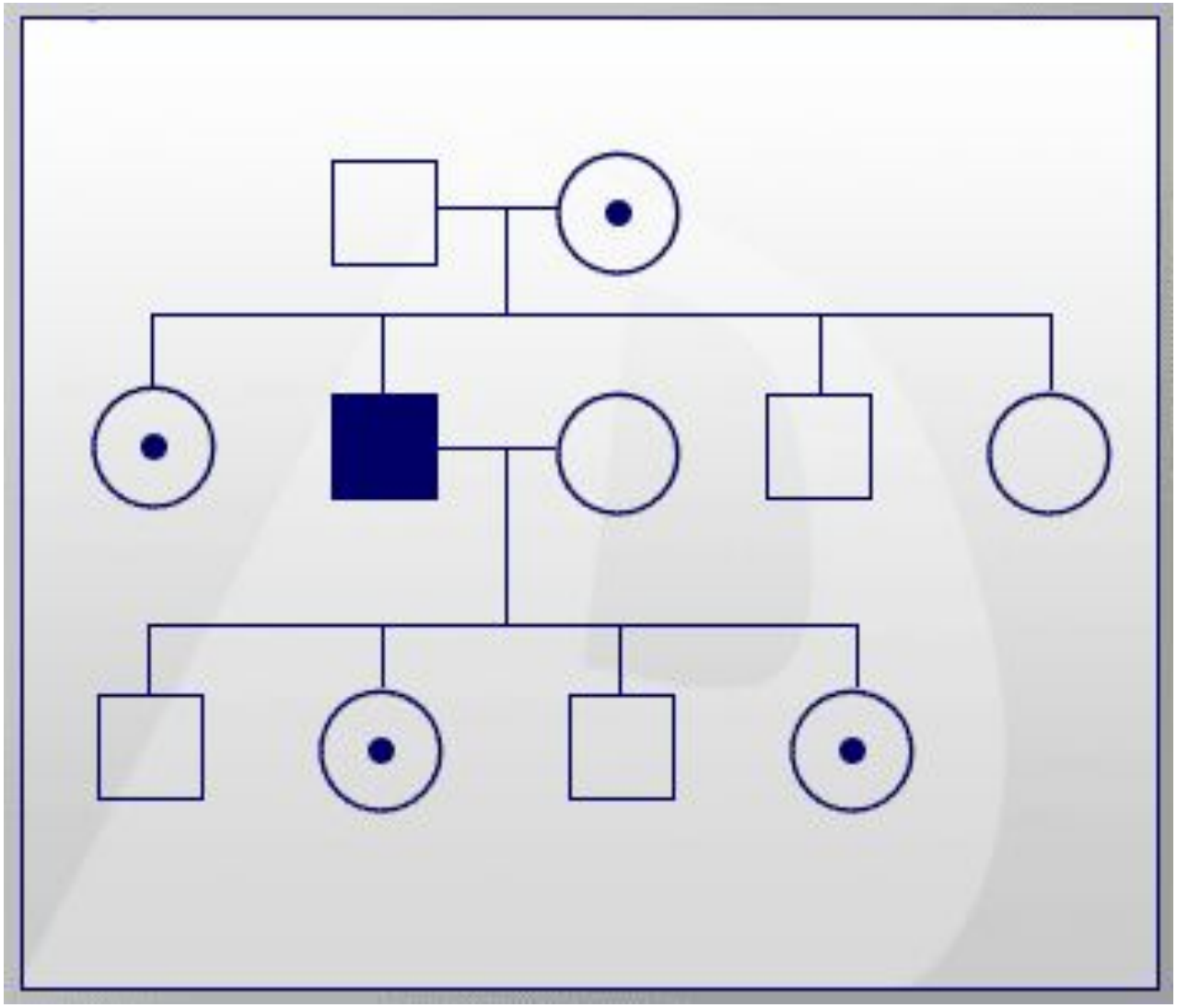
X-linked recessive

- Many more males than females show the disorder.
- All the daughters of an affected male are "carriers".
- None of the sons of an affected male show the disorder or are carriers.
- e.g., hemophilia





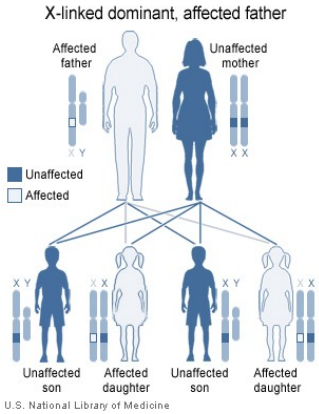


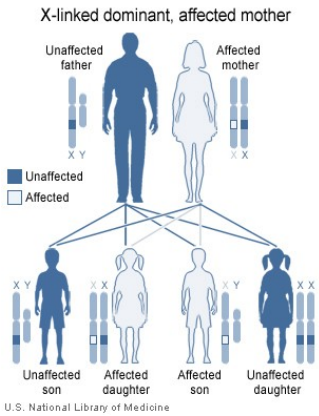


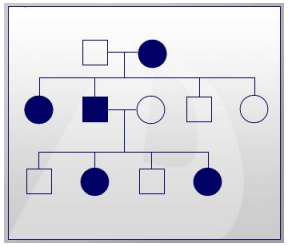
Medical Genetics (cont.)

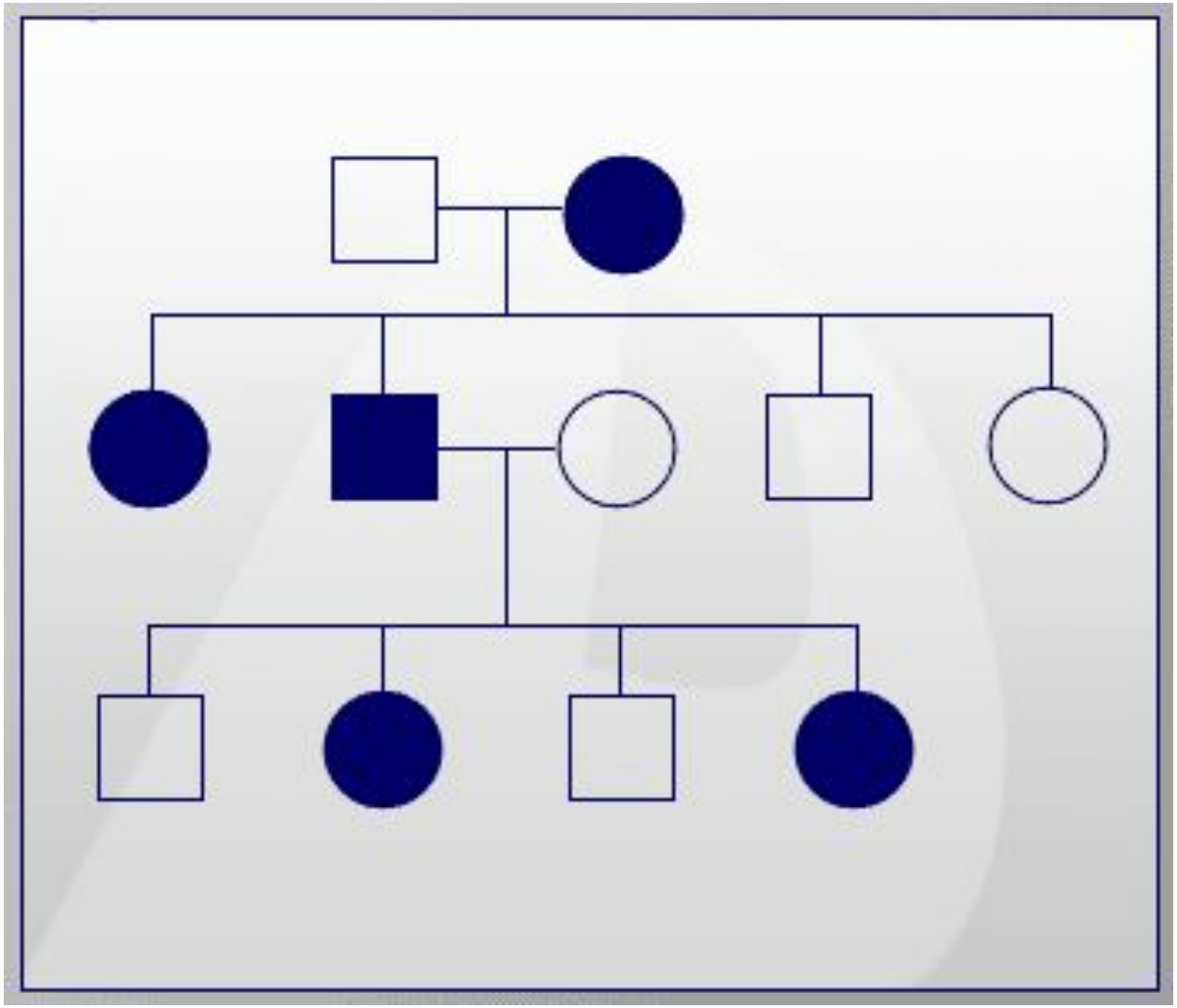
X-linked dominant

- Affected males pass the disorder to all daughters but to none of their sons.
- Affected heterozygous females married to unaffected males pass the condition to half their sons and daughters
- e.g. fragile X syndrome





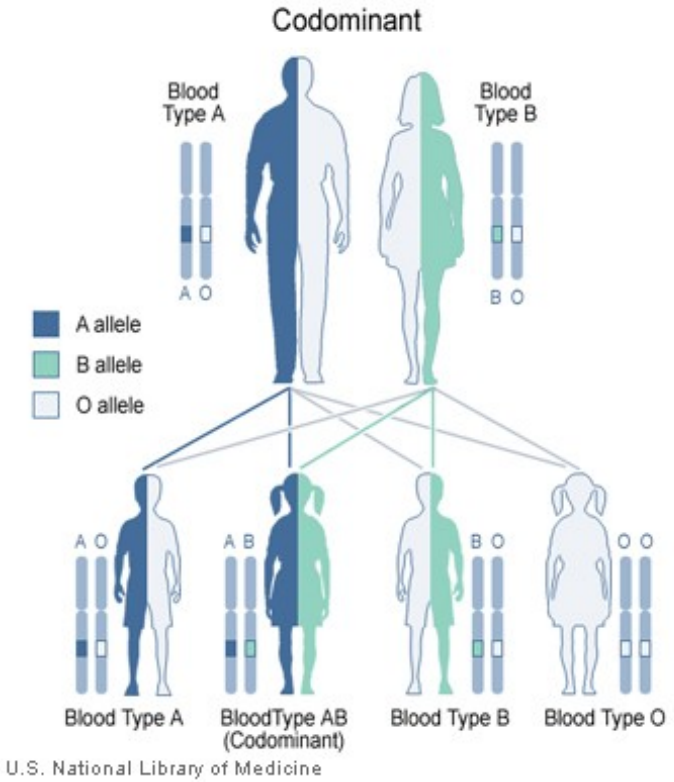




Medical Genetics (cont.)

Codominant inheritance

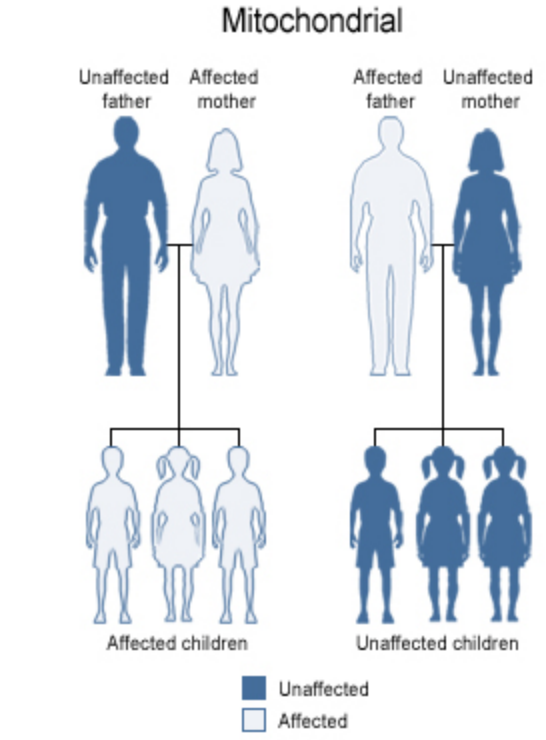
- Two different versions (alleles) of a gene can be expressed, and each version makes a slightly different protein
- Both alleles influence the genetic trait or determine the characteristics of the genetic condition.
- E.g. ABO locus



Medical Genetics (cont.)

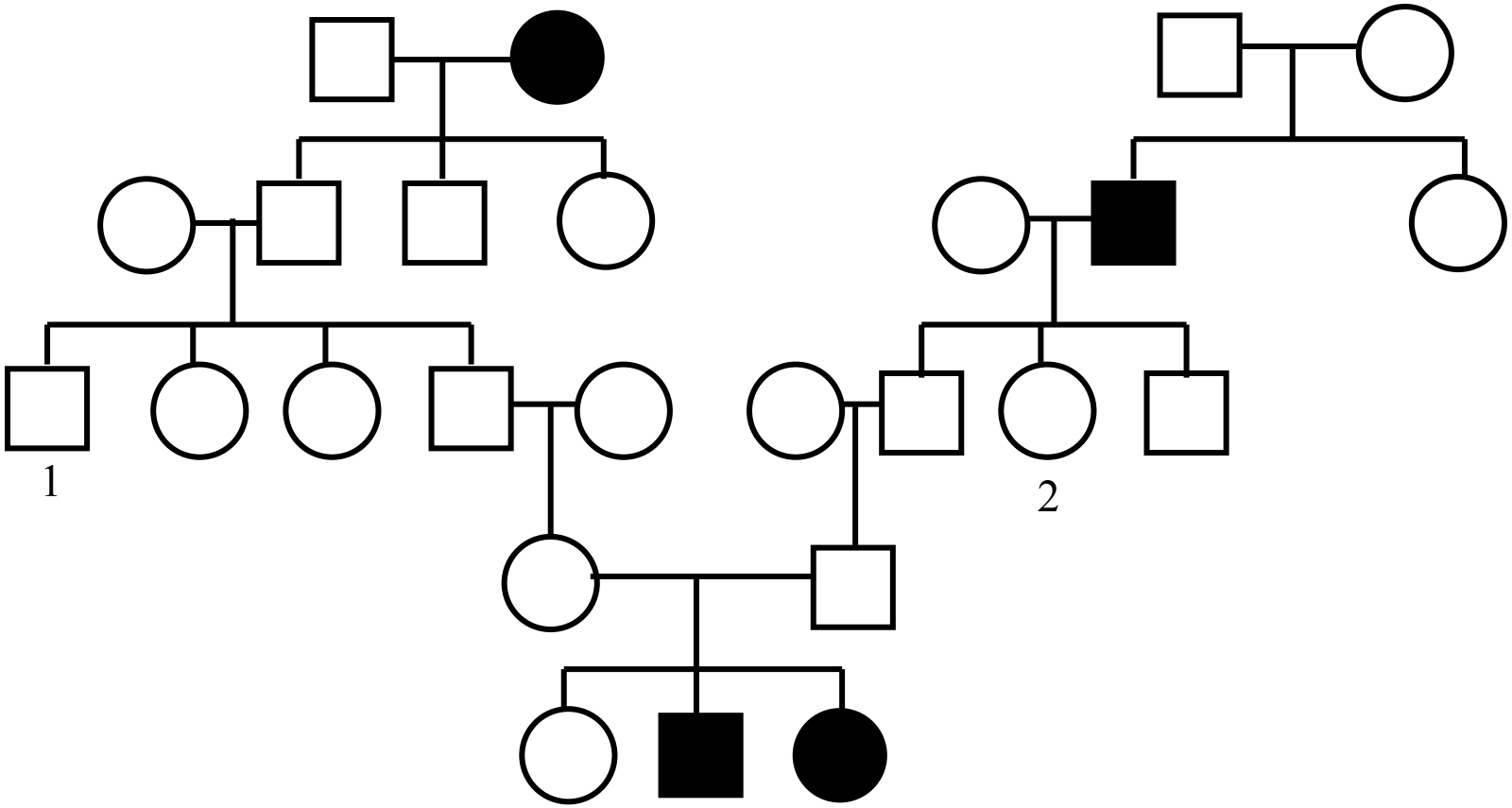
Mitochondrial inheritance

- This type of inheritance applies to genes in mitochondrial DNA
- Mitochondrial disorders can appear in every generation of a family and can affect both males and females, but fathers do not pass mitochondrial traits to their children.
- E.g. Leber's hereditary optic neuropathy (LHON)



U.S. National Library of Medicine

Question #1



Write the genotypes in every possible place.
If individuals 1 and 2 marry, what is the probability that their first child will be sick?

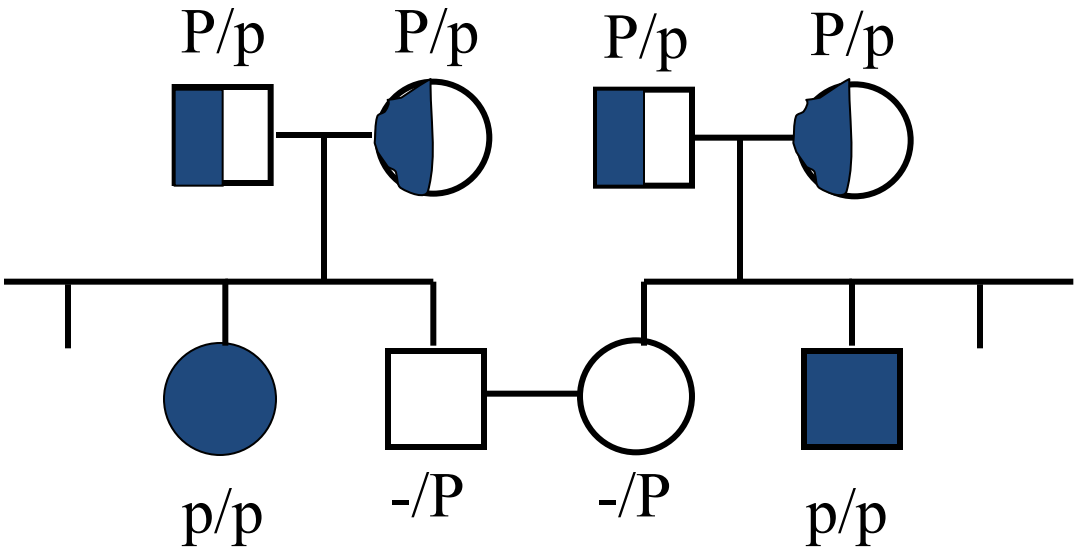
Question #2

- PKU is a human hereditary disease resulting from inability of the body to process the chemical phenylalanine (contained in protein that we eat).

- It is caused by a **recessive allele** with simple Mendelian inheritance.

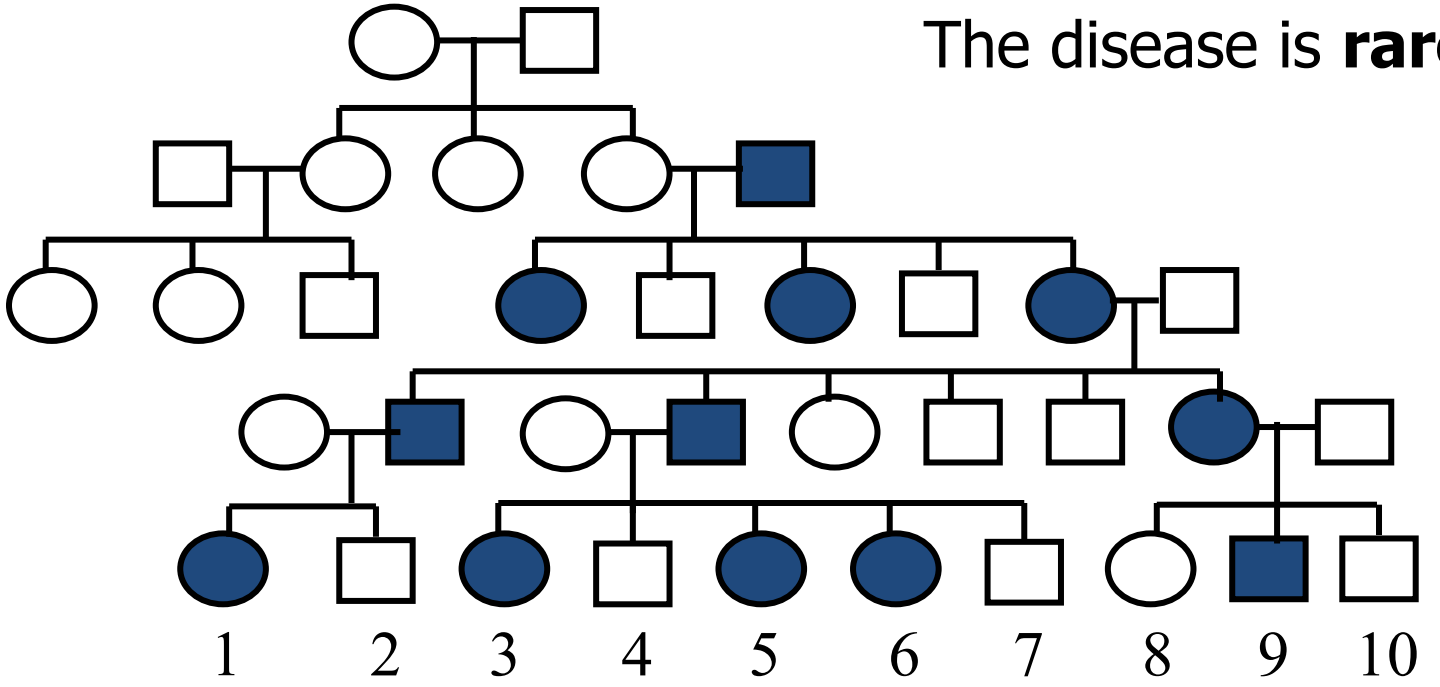
- Some couple wants to have children. The man has a sister with PKU and the woman has a brother with PKU. There are no other known cases in their families.
- **What is the probability that their first child will have PKU ?**

Question #2-Solution Highlights



P – the normal allele
p – the mutant allele

Question #3



The disease is **rare**.

a. What is the most likely mode of inheritance ?

b. What would be the outcomes of the cousin marriages 1 x 9, 1 x 4, 2 x 3, and 2 x 8 ?

Question #3-Solution Highlights

a. Observations:

- After the disease is introduced into the family in generation #2, it appears in every generation **dominant!**
- Fathers do not transmit the phenotype to their sons **X-linked!**

b. The outcomes:

- 1 x 9: 1 must be A/a
  9 must be A/Y
- 1 x 4: 1 must be A/a
  4 must be a/Y
- 2 x 3: 2 must be a/Y
  3 must be A/a

Same

- 2 x 8: 2 must be a/Y
  8 must be a/a

All normal

Notes

- **Cystic fibrosis** – disease affecting the mucus lining of the lungs, leading to breathing problems and other difficulties
- **Huntington disease** - or Huntington's chorea is an inherited disorder characterized by abnormal body movements called chorea, and loss of memory. There also is evidence that doctors as far back as the Middle Ages knew of this devastating disease. The incidence is 5 to 8 per 100,000. It takes its name from the New York physician George Huntington who first described it precisely in 1872.

Notes

- **Hemophilia-illness** that impair the body's ability to control bleeding.
- **Fragile X syndrome** - is a genetic condition that causes a range of developmental problems including learning disabilities and mental retardation. Usually males are more severely affected by this disorder than females. In addition to learning difficulties, affected males tend to be restless, fidgety, and inattentive. Affected males also have characteristic physical features that become more apparent with age.

Notes -cont

- **DNA** - a pair of molecules joined by hydrogen bonds: it is organized as two complementary strands, head-to-toe, with the hydrogen bonds between them. Each strand of DNA is a chain of chemical "building blocks", called nucleotides, of which there are four types:adenide (abbreviated *A*), cytozyne (*C*), guanine (*G*) and thymine (T).

- **Mitochondria**, which are structures in each cell that convert molecules into energy, each contain a small amount of DNA.

- *A* **chromatid** forms one part of a chromosome after it has coalesced for the process of mitosis or meiosis. During either process, the word "chromosome" indicates a pair of two exactly identical ("**sister**") chromatids joined at the central point of each chromatid, called the centromere.

Notes -cont

- **Mitosis** is the process by which a cell separates its duplicated genome into two identical halves
- **Meiosis** is the process that transforms one diploid into four haploid cells.
- **Reciprocal cross** a cross, with the phenotype of each sex reversed as compared with the original cross, to test the role of parental sex on inheritance pattern. A pair of crosses of the type genotype A(female) X genotype B(male) and genotype B(female) X genotype A(male).

2.2 PROBABILITY AND STATISTICS

- The laws of inheritance can be used to predict the outcomes of genetic crosses
- For example
  - Animal and plant breeders are concerned with the types of offspring produced from their crosses
  - Parents are interested in predicting the traits that their children may have
    - This is particularly important in the case of families with genetic diseases

2.2 PROBABILITY AND STATISTICS

- Of course, it is not possible to definitely predict what will happen in the future
- However, genetic counselors can help couples by predicting the likelihood of them having an affected child
  - This probability may influence the couple's decision to have children or not

Probability

- The probability of an event is the chance that the event will occur in the future
- $$\text{Probability} = \frac{\text{Number of times an event occurs}}{\text{Total number of events}}$$
- For example, in a coin flip

$$P_{\text{heads}} = 1 \text{ heads} \,/\, (1 \text{ heads} + 1 \text{ tails}) = 1/2 = 50\%$$

- The accuracy of the probability prediction depends largely on the size of the sample
- Often, there is deviation between observed and expected outcomes
- This is due to random sampling error
  - Random sampling error is large for small samples and small for large samples
- For example
  - If a coin is flipped only 10 times
    - It is not unusual to get 70% heads and 30% tails
  - However, if the coin is flipped 1,000 times
    - The percentage of heads will be fairly close to the predicted 50% value

- Probability calculations are used in genetic problems to predict the outcome of crosses

- To compute probability, we can use three mathematical operations
  - Sum rule
  - Product rule
  - Binomial expansion equation

Sum rule

- The probability that one of two or more mutually exclusive events will occur is the sum of their respective probabilities

- Consider the following example in mice
  - Gene affecting the ears
    - *De* = Normal allele
    - *de* = Droopy ears
  - Gene affecting the tail
    - *Ct* = Normal allele
    - *ct* = Crinkly tail

- If two heterozygous (*Dede Ctct)* mice are crossed
- Then the predicted ratio of offspring is
  - 9 with normal ears and normal tails
  - 3 with normal ears and crinkly tails
  - 3 with droopy ears and normal tails
  - 1 with droopy ears and crinkly tail
- These four phenotypes are mutually exclusive
  - A mouse with droopy ears and a normal tail *cannot* have normal ears and a crinkly tail
- Question
  - What is the probability that an offspring of the above cross will have normal ears and a normal tail ***or*** have droopy ears and a crinkly tail?

- Applying the sum rule
  - Step 1: Calculate the individual probabilities

$$P_{(\text{normal ears and a normal tail})} = 9 / (9 + 3 + 3 + 1) = 9/16$$

$$P_{(\text{droopy ears and crinkly tail})} = 1 / (9 + 3 + 3 + 1) = 1/16$$

  - Step 2: Add the individual probabilities

$$9/16 + 1/16 = 10/16$$

- 10/16 can be converted to 0.625
  - Therefore 62.5% of the offspring are predicted to have normal ears and a normal tail *or* droopy ears and a crinkly tail

Product rule

- The probability that two or more independent events will occur is equal to the product of their respective probabilities

- Note
  - Independent events are those in which the occurrence of one does not affect the probability of another

- Consider the disease congenital analgesia
  - Recessive trait in humans
  - Affected individuals can distinguish between sensations
    - However, extreme sensations are not perceived as painful
  - Two alleles
    - *P* = Normal allele
    - *p* = Congenital analgesia

- Question
  - Two heterozygous individuals plan to start a family
  - What is the probability that the couple's first three children will all have congenital analgesia?

- Applying the product rule
  - Step 1: Calculate the individual probabilities
    - This can be obtained via a Punnett square

$$P_{(\text{congenital analgesia})} = 1/4$$

  - Step 2: Multiply the individual probabilities

$$1/4 \times 1/4 \times 1/4 = 1/64$$

- 1/64 can be converted to 0.016
  - Therefore 1.6% of the time, the first three offspring of a heterozygous couple, will all have congenital analgesia

Binomial Expansion Equation

- Represents all of the possibilities for a given set of unordered events

$$P = \frac{n!}{x!\,(n-x)!}\, p^{x}\, q^{n-x}$$

- where
  - p = probability that the unordered number of events will occur
  - n = total number of events
  - x = number of events in one category
  - p = individual probability of x
  - q = individual probability of the other category

- Note:
  - p + q = 1
  - The symbol ! denotes a factorial
    - n! is the product of all integers from n down to 1
      - 4! = 4 X 3 X 2 X 1 = 24
      - An exception is 0! = 1

- Question
  - Two heterozygous brown-eyed (*Bb*) individuals have five children
  - What is the probability that two of the couple's five children will have blue eyes?

- Applying the binomial expansion equation
  - Step 1: Calculate the individual probabilities
    - This can be obtained via a Punnett square

$$P_{(\text{blue eyes})} = p = 1/4$$

$$P_{(\text{brown eyes})} = q = 3/4$$

  - Step 2: Determine the number of events
    - n = total number of children = 5
    - x = number of blue-eyed children = 2

  - Step 3: Substitute the values for *p*, *q*, *x*, and *n* in the binomial expansion equation

$$P = \frac{n!}{x!\,(n-x)!}\, p^{x}\, q^{n-x}$$

$$P = \frac{5!}{2!\,(5-2)!}\, (1/4)^{2}\, (3/4)^{5-2}$$

$$P = \frac{5 \text{ X } 4 \text{ X } 3 \text{ X } 2 \text{ X } 1}{(2 \text{ X } 1)\ (3 \text{ X } 2 \text{ X } 1)}\, (1/16)\, (27/64)$$

$$P = 0.26 \quad \text{or } 26\%$$

- Therefore 26% of the time, a heterozygous couple's five children will contain two with blue eyes and three with brown eyes

The Chi Square Test

- A statistical method used to determine goodness of fit
  - Goodness of fit refers to how close the observed data are to those predicted from a hypothesis

- Note:
  - The chi square test does not prove that a hypothesis is correct
    - It evaluates whether or not the data and the hypothesis have a good fit

The Chi Square Test

- The general formula is

$$\chi^2 = \Sigma \frac{(O - E)^2}{E}$$

- where
  - O = observed data in each category
  - E = observed data in each category based on the experimenter's hypothesis
  - Σ = Sum of the calculations for each category

- Consider the following example in *Drosophila melanogaster*
  - Gene affecting wing shape
    - c^+ = Normal wing
    - c = Curved wing
  - Gene affecting body color
    - e^+ = Normal (gray)
    - e = ebony
  - Note:
    - The wild-type allele is designated with a + sign
    - Recessive mutant alleles are designated with lowercase letters
- The Cross:
  - A cross is made between two true-breeding flies ($c^+c^+e^+e^+$ and *ccee).* The flies of the F_1 generation are then allowed to mate with each other to produce an F_2 generation.

- The outcome
  - F_1 generation
    - All offspring have straight wings and gray bodies
  - F_2 generation
    - 193 straight wings, gray bodies
    - 69 straight wings, ebony bodies
    - 64 curved wings, gray bodies
    - 26 curved wings, ebony bodies
    - 352 total flies

- Applying the chi square test
  - Step 1: Propose a hypothesis that allows us to calculate the expected values based on Mendel's laws
    - The two traits are independently assorting

- Step 2: Calculate the expected values of the four phenotypes, based on the hypothesis
  - According to our hypothesis, there should be a 9:3:3:1 ratio on the F_2 generation

Phenotype	Expected probability	Expected number
straight wings, gray bodies	9/16	9/16 X 352 = 198
straight wings, ebony bodies	3/16	3/16 X 352 = 66
curved wings, gray bodies	3/16	3/16 X 352 = 66
curved wings, ebony bodies	1/16	1/16 X 352 = 22

- Step 3: Apply the chi square formula

$$\chi^2 = \frac{(O_1 - E_1)^2}{E_1} + \frac{(O_2 - E_2)^2}{E_2} + \frac{(O_3 - E_3)^2}{E_3} + \frac{(O_4 - E_4)^2}{E_4}$$

$$\chi^2 = \frac{(193 - 198)^2}{198} + \frac{(69 - 66)^2}{66} + \frac{(64 - 66)^2}{66} + \frac{(26 - 22)^2}{22}$$

$$\chi^2 = 0.13 + 0.14 + 0.06 + 0.73$$

$$\chi^2 = 1.06$$

- Step 4: Interpret the chi square value
  - The calculated chi square value can be used to obtain probabilities, or P values, from a chi square table
    - These probabilities allow us to determine the likelihood that the observed deviations are due to random chance alone
  - Low chi square values indicate a high probability that the observed deviations could be due to random chance alone
  - High chi square values indicate a low probability that the observed deviations are due to random chance alone
  - If the chi square value results in a probability that is less than 0.05 (ie: less than 5%)
    - The hypothesis is rejected

- Step 4: Interpret the chi square value

  - Before we can use the chi square table, we have to determine the degrees of freedom (*df*)
    - The *df* is a measure of the number of categories that are independent of each other
    - $df = n - 1$
      - where n = total number of categories
    - In our experiment, there are four phenotypes/categories
      - Therefore, df = 4 – 1 = 3

  - Refer to Table 2.1

TABLE 2.1

Chi Square Values and Probability

Degrees of Freedom	$P = 0.99$	0.95	0.80	0.50	0.20	0.05	0.01
1	0.000157	0.00393	0.0642	0.455	1.642	**3.841**	**6.635**
2	0.020	0.103	0.446	1.386	3.219	**5.991**	**9.210**
3	0.115	0.352	1.005	2.366	4.642	**7.815**	**11.345**
4	0.297	0.711	1.649	3.357	5.989	**9.488**	**13.277**
5	0.554	1.145	2.343	4.351	7.289	**11.070**	**15.086**
6	0.872	1.635	3.070	5.348	8.558	**12.592**	**16.812**
7	1.239	2.167	3.822	6.346	9.803	**14.067**	**18.475**
8	1.646	2.733	4.594	7.344	11.030	**15.507**	**20.090**
9	2.088	3.325	5.380	8.343	12.242	**16.919**	**21.666**
10	2.558	3.940	6.179	9.342	13.442	**18.307**	**23.209**
15	5.229	7.261	10.307	14.339	19.311	**24.996**	**30.578**
20	8.260	10.851	14.578	19.337	25.038	**31.410**	**37.566**
25	11.524	14.611	18.940	24.337	30.675	**37.652**	**44.314**
30	14.953	18.493	23.364	29.336	36.250	**43.773**	**50.892**

1.06

From Fisher, R. A., and Yates, F. (1943) *Statistical Tables for Biological, Agricultural, and Medical Research.* Oliver and Boyd, London.

- Step 4: Interpret the chi square value

  - With *df* = *3,* the chi square value of 1.06 is slightly greater than 1.005 (which corresponds to P= 0.80)

  - A P = 0.80 means that values equal to or greater than 1.005 are expected to occur 80% of the time based on random chance alone

  - Therefore, it is quite probable that the deviations between the observed and expected values in this experiment can be explained by random sampling error