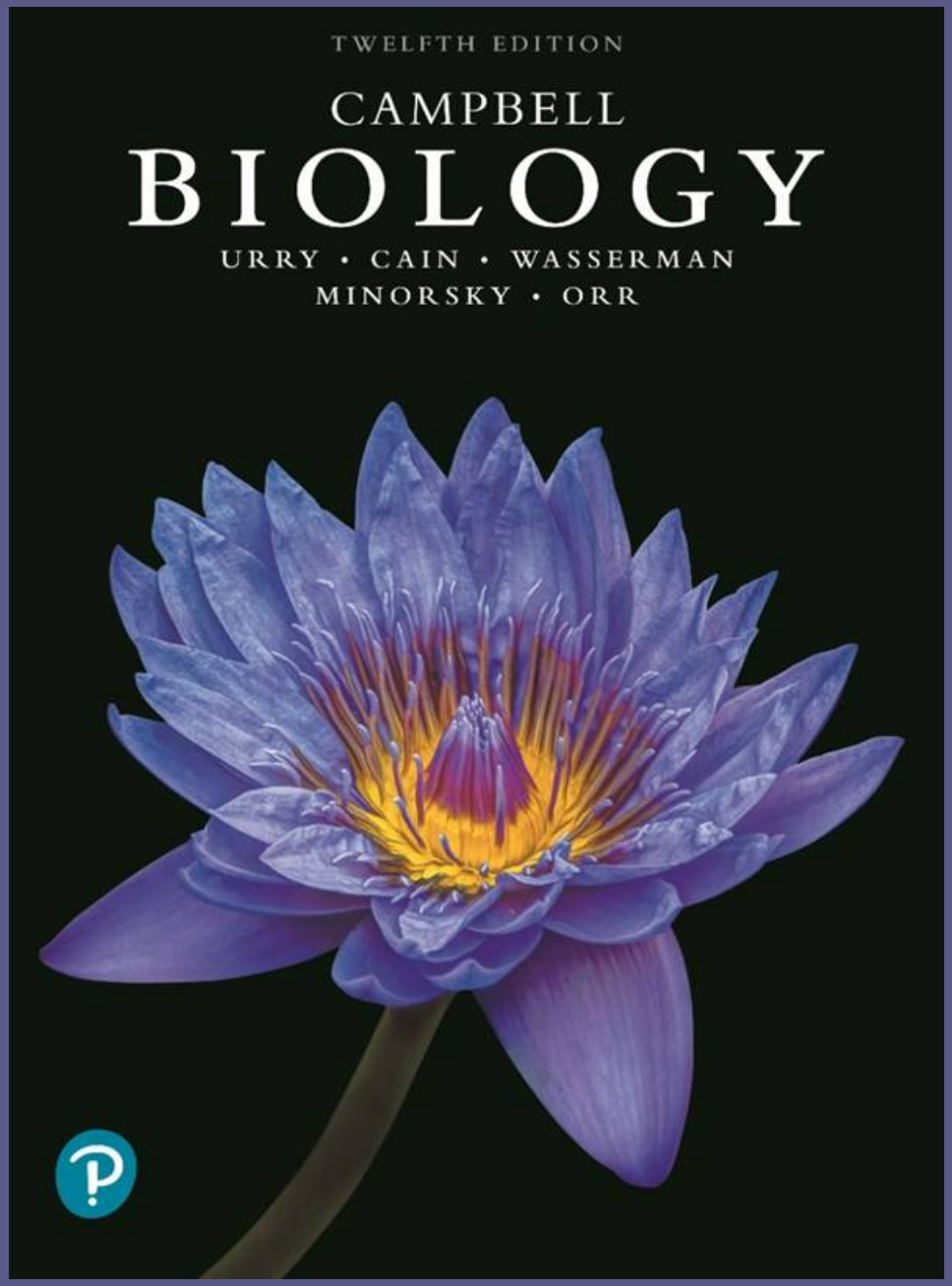


Chapter 15

The Chromosomal Basis of Inheritance

Lecture Presentations by
Nicole Tunbridge and
Kathleen Fitzpatrick

Figure 15.1a

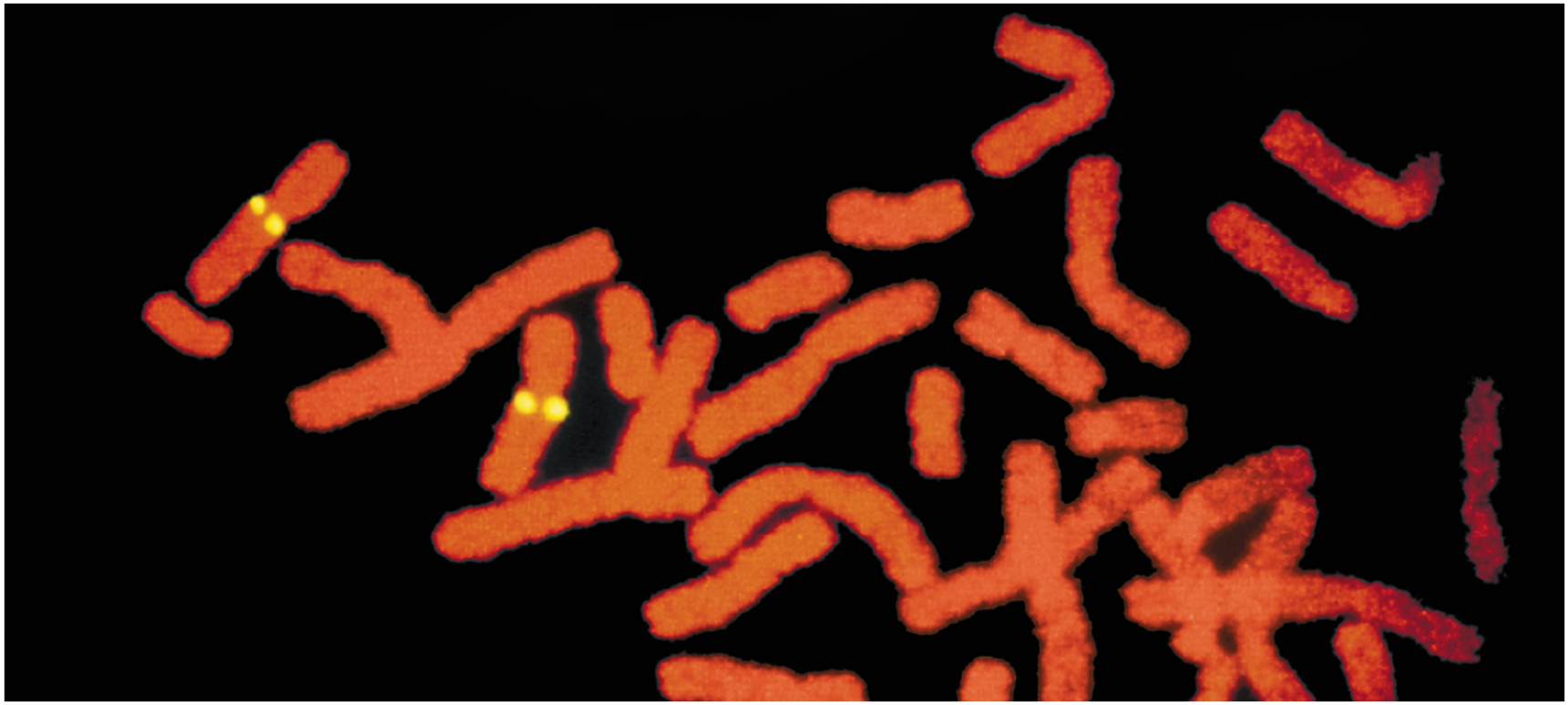


Figure 15.1b

What is the relationship between genes and chromosomes?

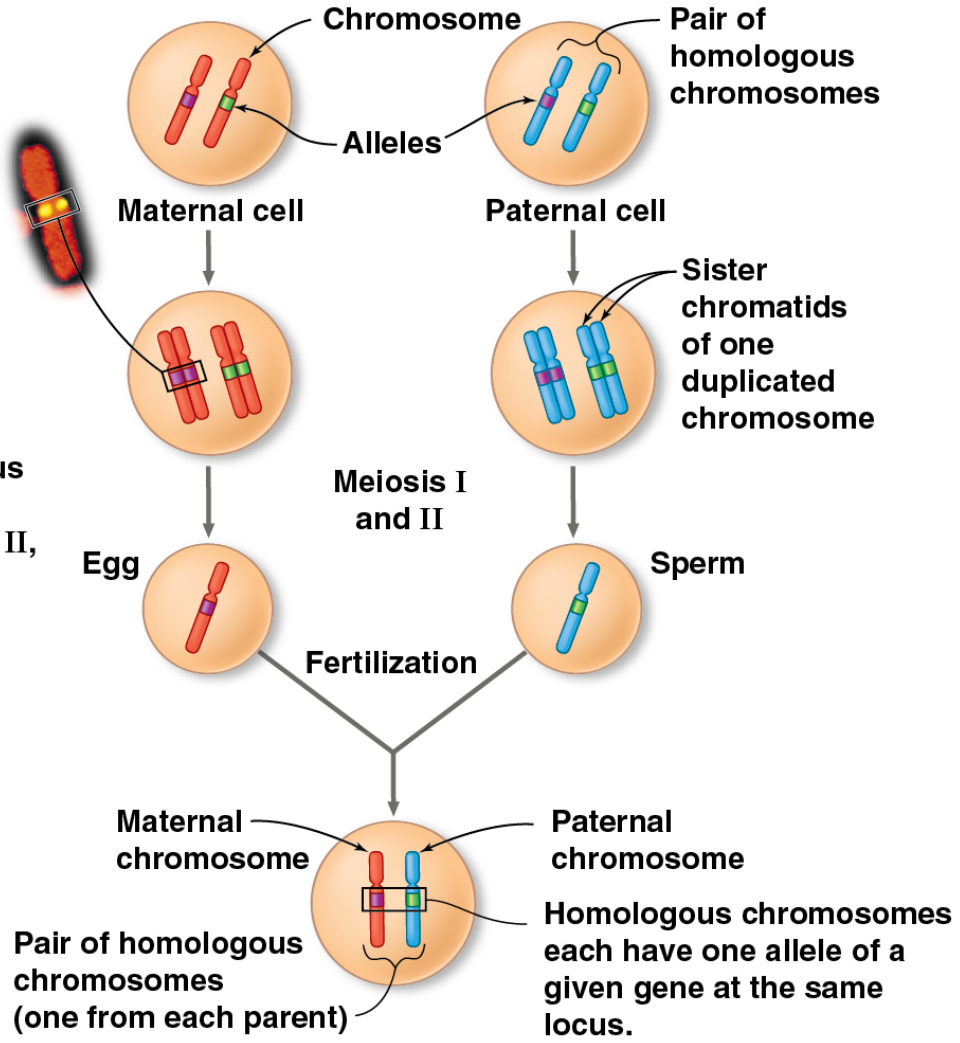
Genes are located on chromosomes.

Chromosomes duplicate before cell division.

During meiosis I, homologous chromosomes separate and alleles segregate. In meiosis II, sister chromatids separate.

Each chromosome has one version of a gene (one allele).

Offspring inherit one allele from each parent.



Concept 15.1: Mendelian inheritance has its physical basis in the behavior of chromosomes

- Mendel's proposed "hereditary units" were only theoretical in 1860
- Soon, biologists saw parallels between chromosome behavior and the behavior of the proposed factors
- Around 1902, Sutton and Boveri and others independently noted these parallels and began to develop the **chromosome theory of inheritance**

- The first solid evidence associating a specific gene with a specific chromosome came in the early 1900s from the work of Thomas Hunt Morgan
- His early experiments provided convincing evidence that the chromosomes are the location of Mendel's heritable factors

Morgan's Choice of Experimental Organism

- For his work, Morgan chose to study *Drosophila melanogaster*, a common species of fruit fly
- Several characteristics make fruit flies a convenient organism for genetic studies:
  - They produce many offspring
  - A generation can be bred every two weeks
  - They have only four pairs of chromosomes

- Morgan noted **wild type**, or normal, phenotypes that were common in the fly populations
- Traits alternative to the wild type are called mutant phenotypes
- The first mutant Morgan discovered was a fly with white eyes instead of the wild-type red eyes

Figure 15.2

Wild type (red eyes)

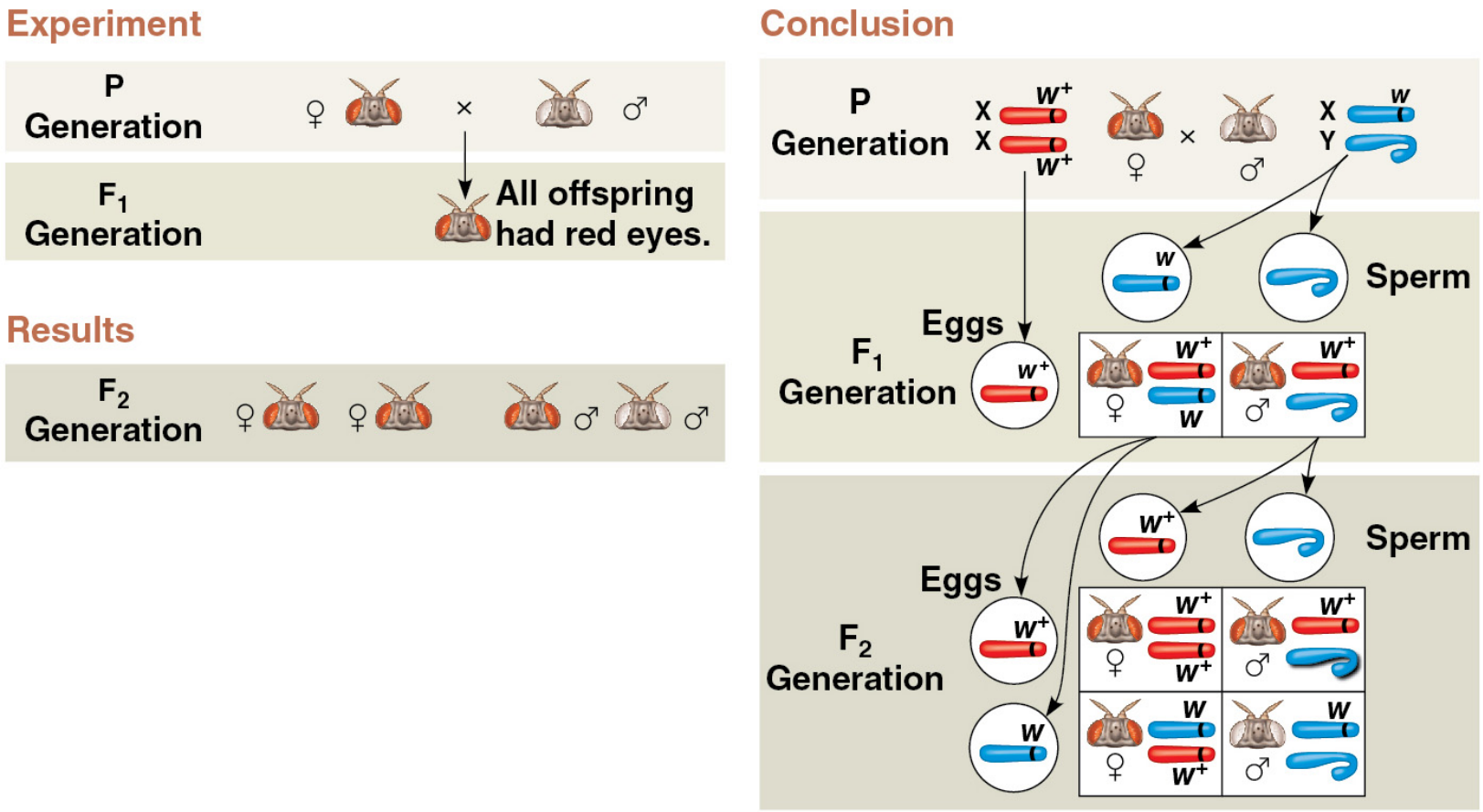
Mutant (white eyes)

Correlating Behavior of a Gene's Alleles with Behavior of a Chromosome Pair: *Scientific Inquiry*

- In one experiment, Morgan mated male flies with white eyes (mutant) with female flies with red eyes (wild type)
  - The F_1 generation all had red eyes
  - The F_2 generation showed a 3:1 red to white eye ratio, but only males had white eyes

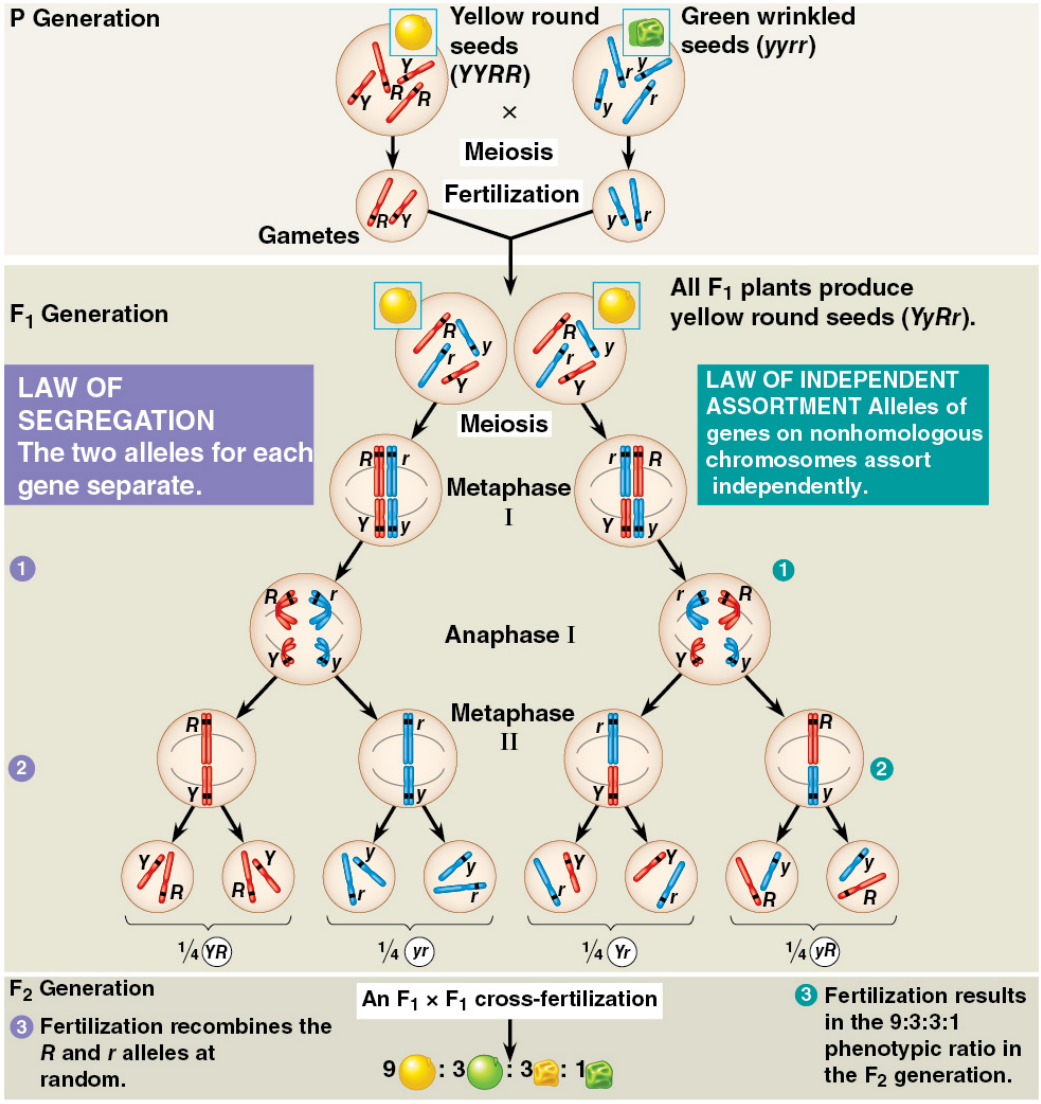
- Morgan reasoned that the white-eyed mutant allele must be located on the X chromosome
- Female flies have two X chromosomes (XX) while males have one X and one Y (XY)
- Morgan's finding supported the chromosome theory of inheritance

Figure 15.3



Data from T. H. Morgan, Sex-limited inheritance in *Drosophila*, *Science* 32:120–122 (1910).

Figure 15.4


P Generation
Yellow round seeds (YYRR)
×
Green wrinkled seeds (yyrr)
Meiosis
Fertilization
Gametes
F1 Generation
All F1 plants produce yellow round seeds (YyRr).
LAW OF SEGREGATION
The two alleles for each gene separate.
LAW OF INDEPENDENT ASSORTMENT Alleles of genes on nonhomologous chromosomes assort independently.
Meiosis
Metaphase I
Anaphase I
Metaphase II
1/4 (YR)
1/4 (yr)
1/4 (Yr)
1/4 (yR)
F2 Generation
3 Fertilization recombines the R and r alleles at random.
An F1 × F1 cross-fertilization
9 : 3 : 3 : 1
3 Fertilization results in the 9:3:3:1 phenotypic ratio in the F2 generation.

Concept 15.2: Sex-linked genes exhibit unique patterns of inheritance

- Morgan's discovery of a trait that correlated with the sex of flies was key to the development of the chromosome theory of inheritance

The Chromosomal Basis of Sex

- Humans and other mammals have two types of sex chromosomes: a larger X chromosome and a smaller Y chromosome
- A person with two X chromosomes usually develops anatomy we associate with the “female” sex
- “Male” properties are associated with the inheritance of one X and one Y
- The X-Y system is not the only chromosomal system of sex determination

Figure 15.5

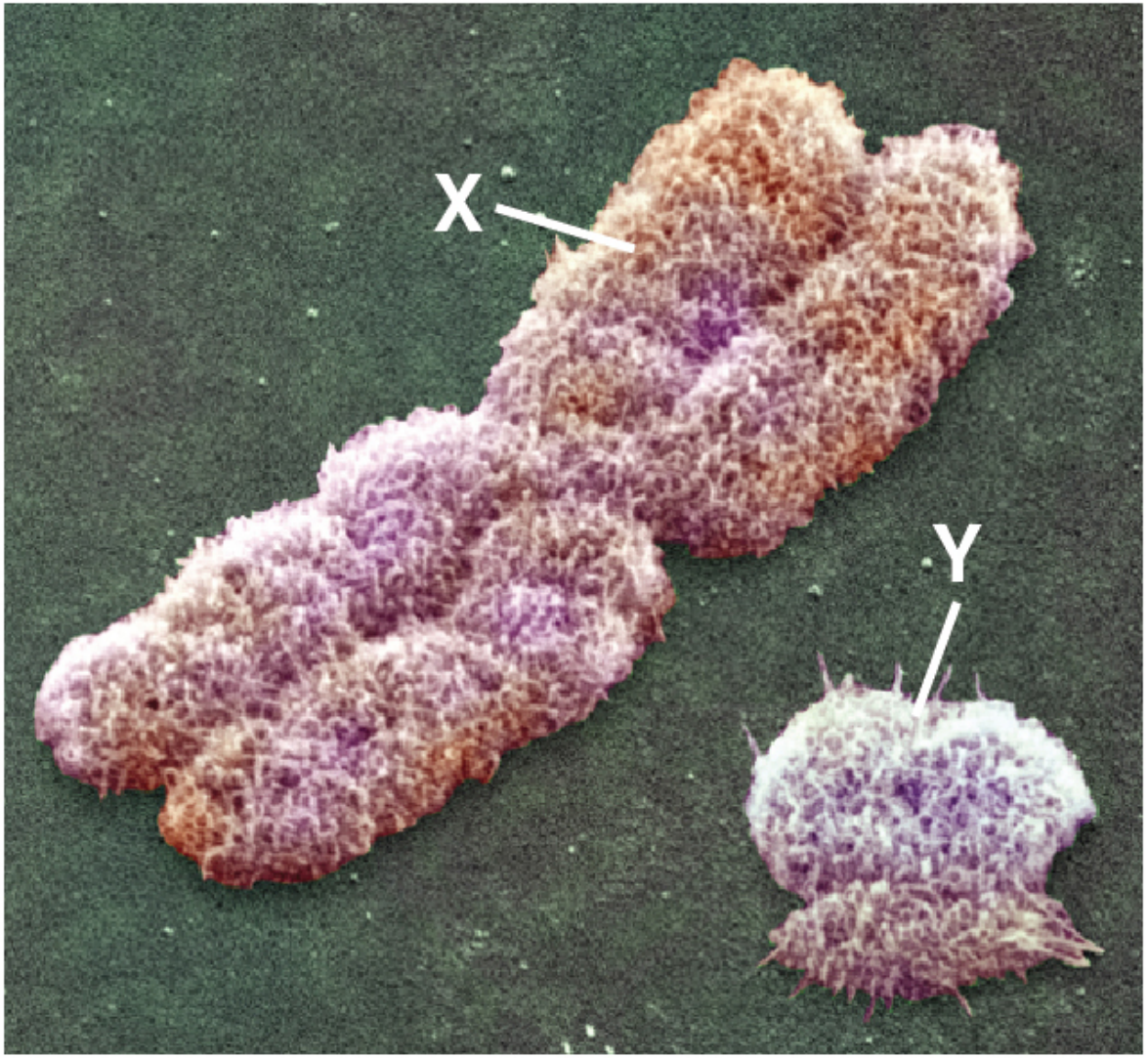
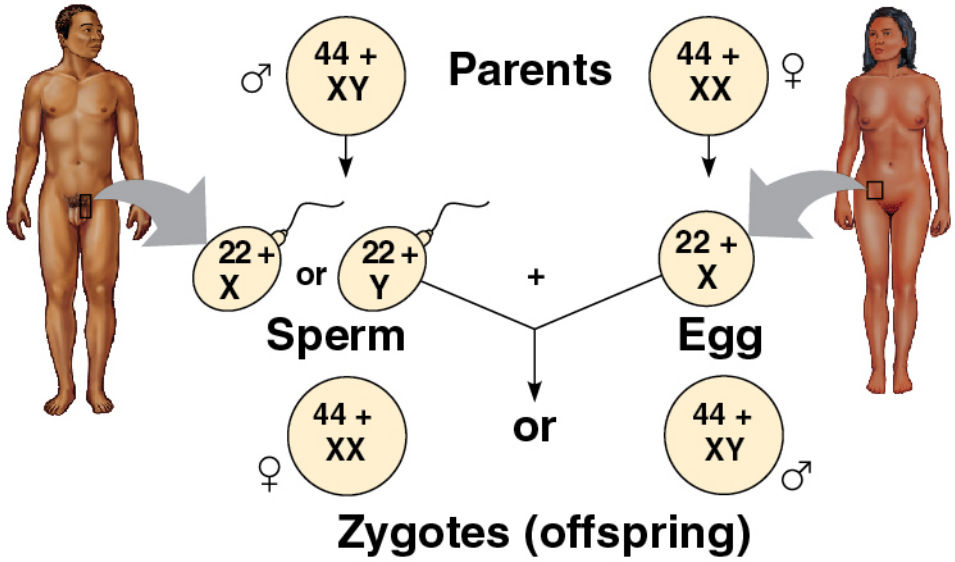


Figure 15.6



(a) The X-Y system

76 + ZW
♀

76 + ZZ
♂

(c) The Z-W system

22 + XX
♀

22 + X
♂

(b) The X-0 system

32 (Diploid)
♀

16 (Haploid)
♂

(d) The haplo-diploid system

- Short segments at the ends of the Y chromosomes are homologous with the X, allowing the two to behave like homologs during meiosis in males
- In mammals, a gene on the Y chromosome called *SRY* (sex-determining region on the Y) is responsible for development of the testes in an embryo

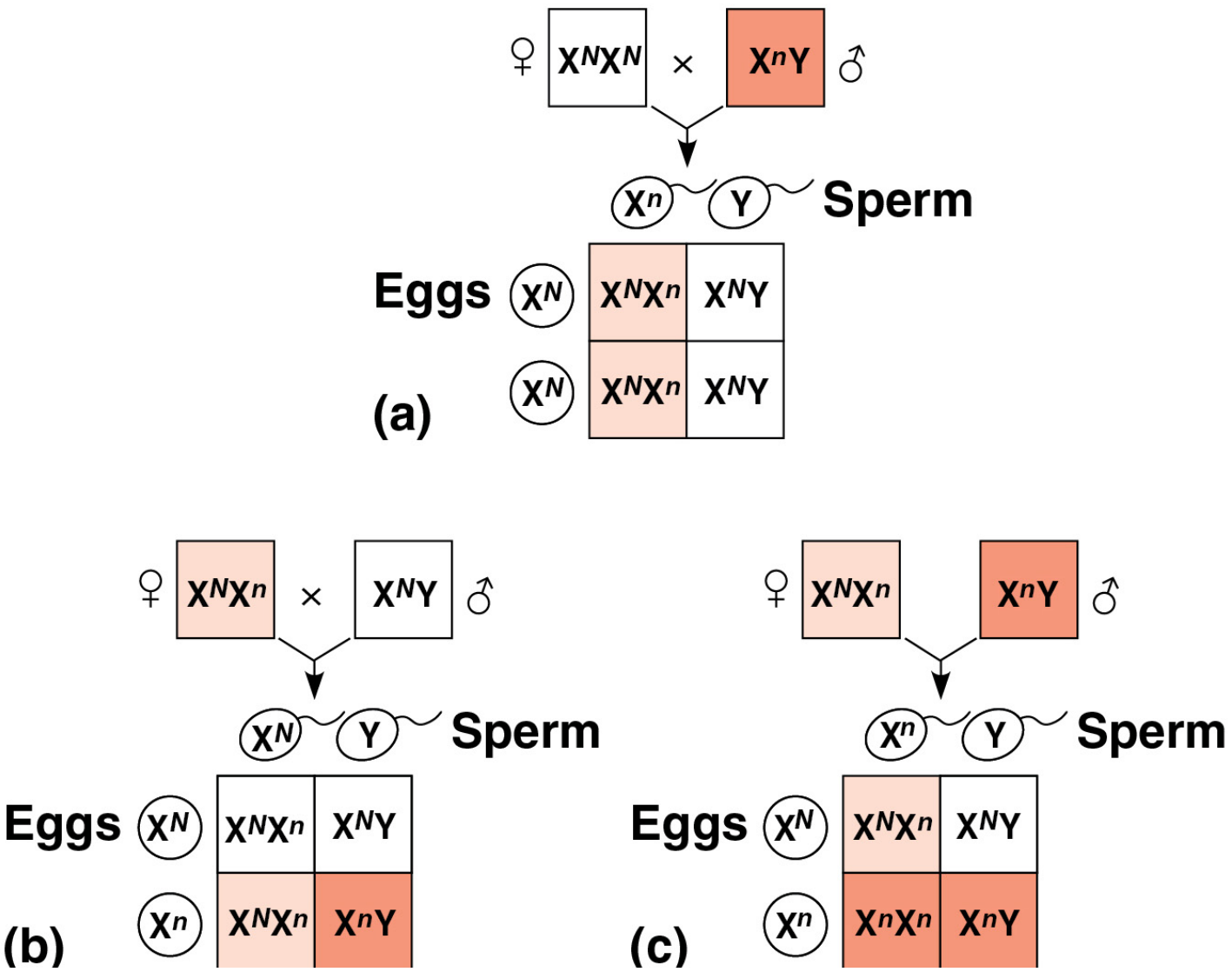
- A gene that is located on either sex chromosome is called a **sex-linked gene**
- Genes on the Y chromosome are called Y-linked genes
- Only 78 genes, coding for about 25 proteins, have been identified on the human Y chromosome
- Genes on the X chromosome are called **X-linked genes**; the human X chromosome contains about 1,100 genes

Inheritance of X-Linked Genes

- X chromosomes have genes for many characters unrelated to sex
- Many Y-linked genes are related to sex determination

- X-linked genes follow a specific pattern of inheritance
- For a recessive X-linked trait to be expressed,
  - a female needs two copies of the allele (homozygous)
  - a male needs only one copy of the allele (hemizygous)
- X-linked recessive disorders are much more common in males than in females

Figure 15.7


♀ X^NX^N × X^nY ♂
X^n Y Sperm
Eggs
X^N X^NX^n X^NY
X^N X^NX^n X^NY
(a)
♀ X^NX^n × X^NY ♂
X^N Y Sperm
Eggs
X^N X^NX^n X^NY
X^n X^NX^n X^nY
(b)
♀ X^NX^n X^nY ♂
X^n Y Sperm
Eggs
X^N X^NX^n X^NY
X^n X^nX^n X^nY
(c)

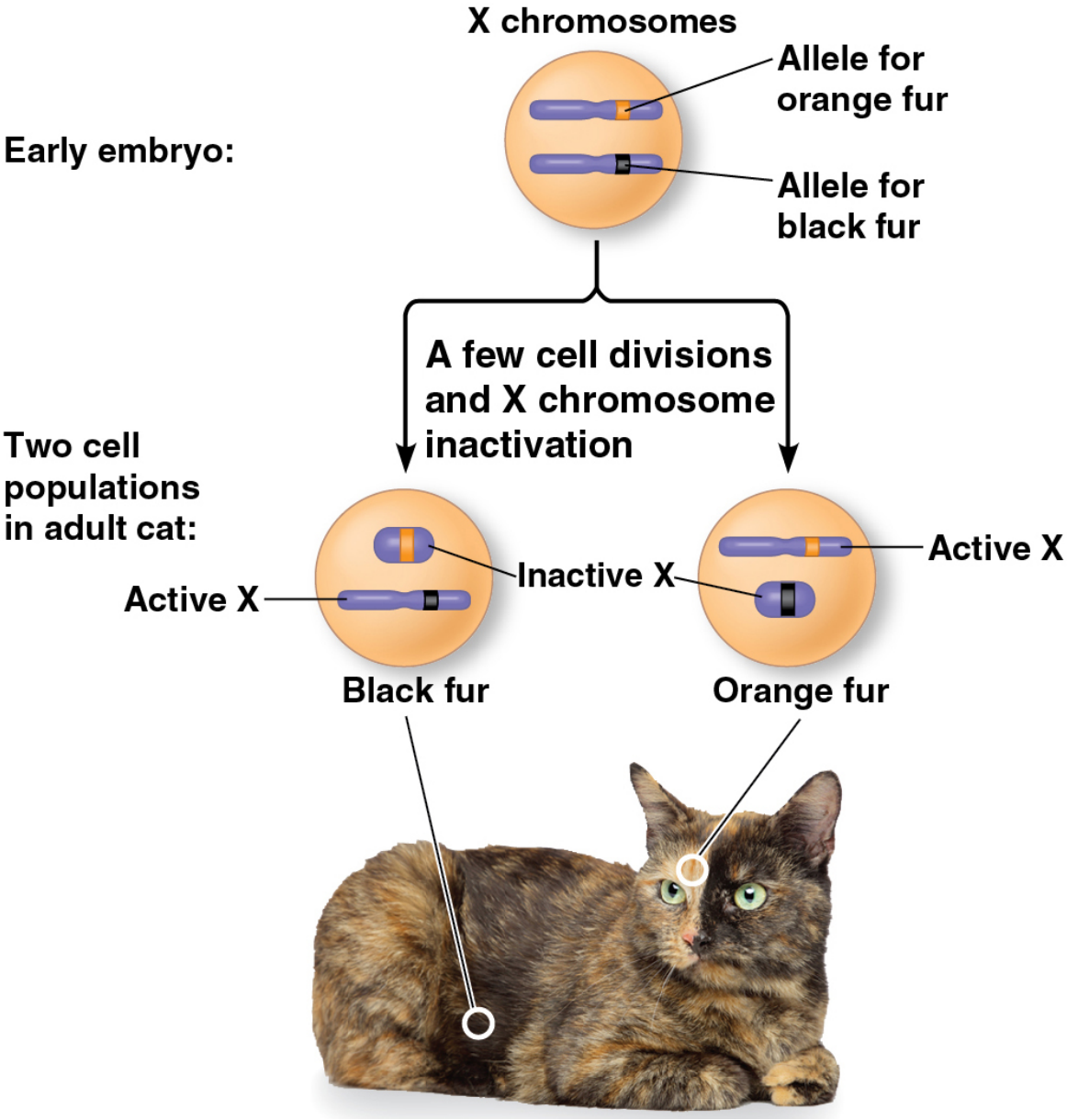
- Some disorders caused by recessive alleles on the X chromosome in humans:
  - Color blindness (mostly X-linked)
  - **Duchenne muscular dystrophy**
  - **Hemophilia**

X Inactivation in Female Mammals

- In mammalian females, one of the two X chromosomes in each cell is randomly inactivated during embryonic development
- The inactive X condenses into a **Barr body**
- If a female is heterozygous for a particular gene located on the X chromosome, she will be a mosaic for that character

- Inactivation of an X chromosome involves modification of the DNA and proteins bound to it called histones
- A part of the chromosome contains several genes involved in the inactivation process
- One of the genes there becomes active only on the chromosome that will be inactivated
- The gene is called *XIST* (X-inactive specific transcript)

Figure 15.8


X chromosomes
Allele for orange fur
Allele for black fur
Early embryo:
A few cell divisions and X chromosome inactivation
Two cell populations in adult cat:
Active X
Inactive X
Active X
Black fur
Orange fur

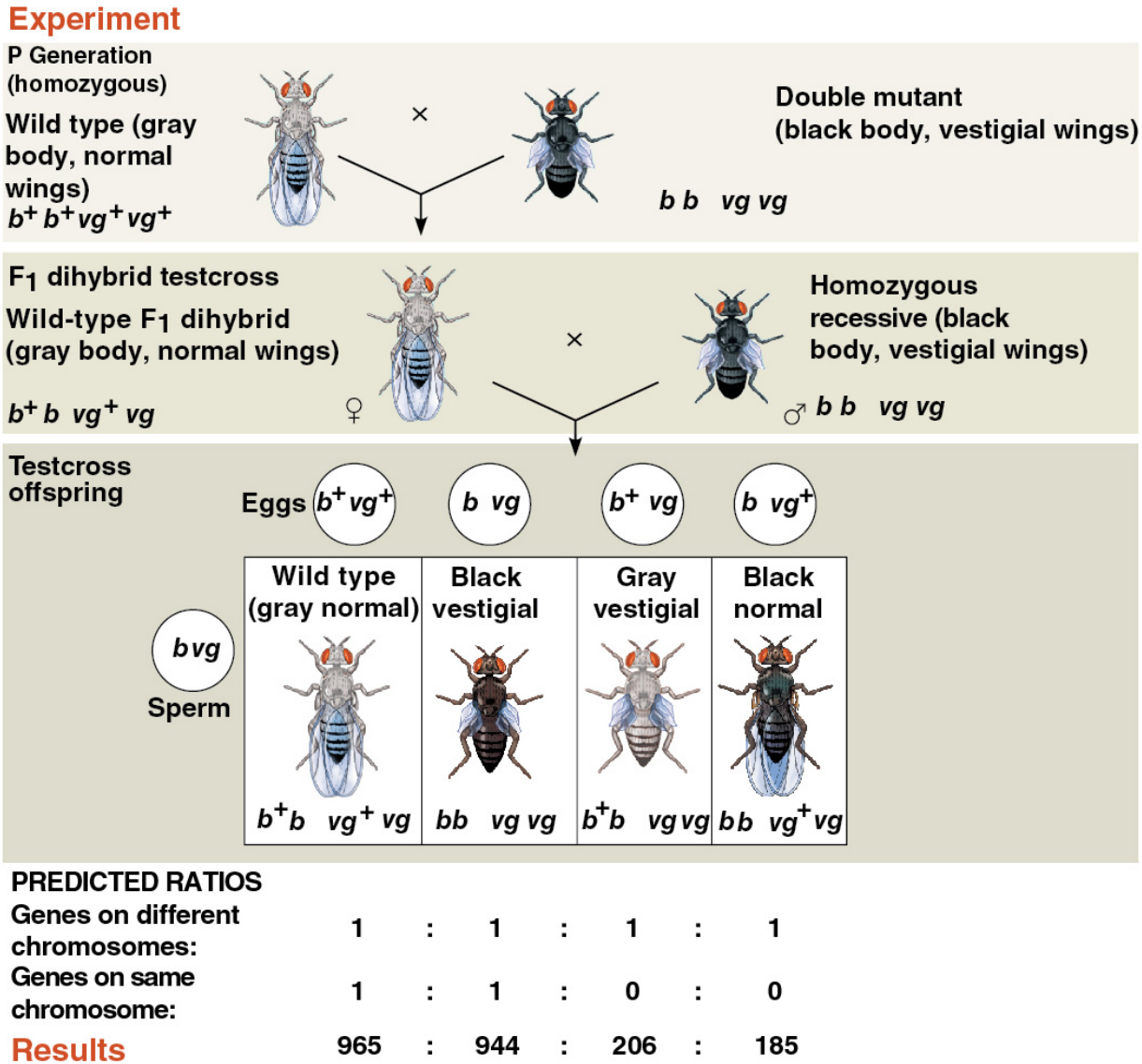
Concept 15.3: Linked genes tend to be inherited together because they are located near each other on the same chromosome

- Each chromosome has hundreds or thousands of genes (except the Y chromosome)
- Genes that are located on the same chromosome tend to be inherited together and are called **linked genes**

How Linkage Affects Inheritance

- Morgan did experiments with fruit flies to see how linkage affects inheritance of two characters
- Morgan crossed flies that differed in traits of body color and wing size
- The first cross was a P generation cross to generate F_1 dihybrid flies
- The second was a testcross

Figure 15.9

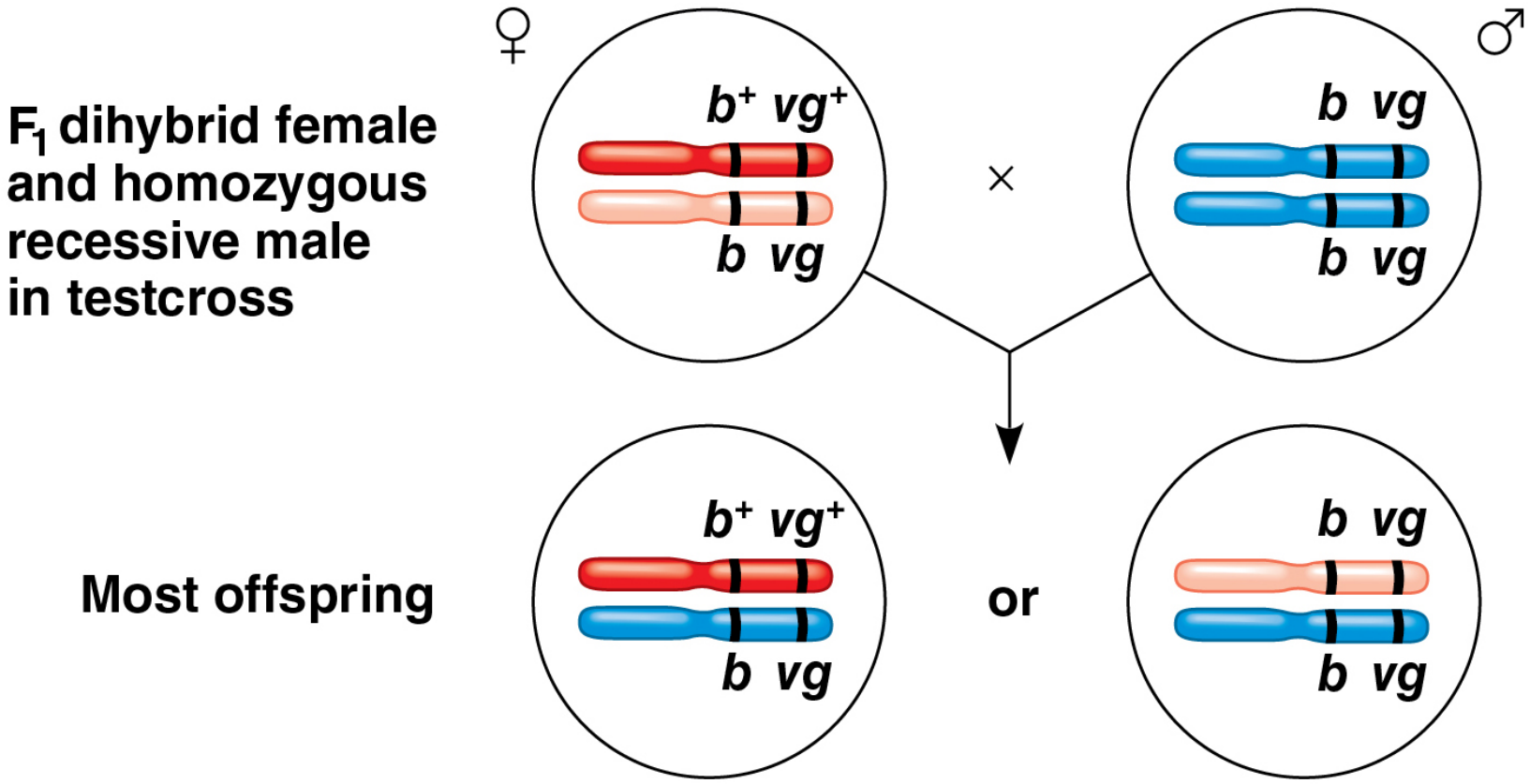


PREDICTED RATIOS								
Genes on different chromosomes:	1	:	1	:	1	:	1
Genes on same chromosome:	1	:	1	:	0	:	0
Results	965	:	944	:	206	:	185

Data from T. H. Morgan and C. J. Lynch, The linkage of two factors in *Drosophila* that are not sex-linked, *Biological Bulletin* 23:174–182 (1912).

- The resulting flies had a much higher than expected proportion of the combination of traits seen in the P generation flies (parental phenotypes)
- He concluded that these genes do not assort independently and reasoned that they were on the same chromosome

Figure 15.UN01



- Nonparental phenotypes were also produced in the testcross, suggesting that the two traits could be separated sometimes
- This involves **genetic recombination**, the production of offspring with combinations of traits differing from either parent

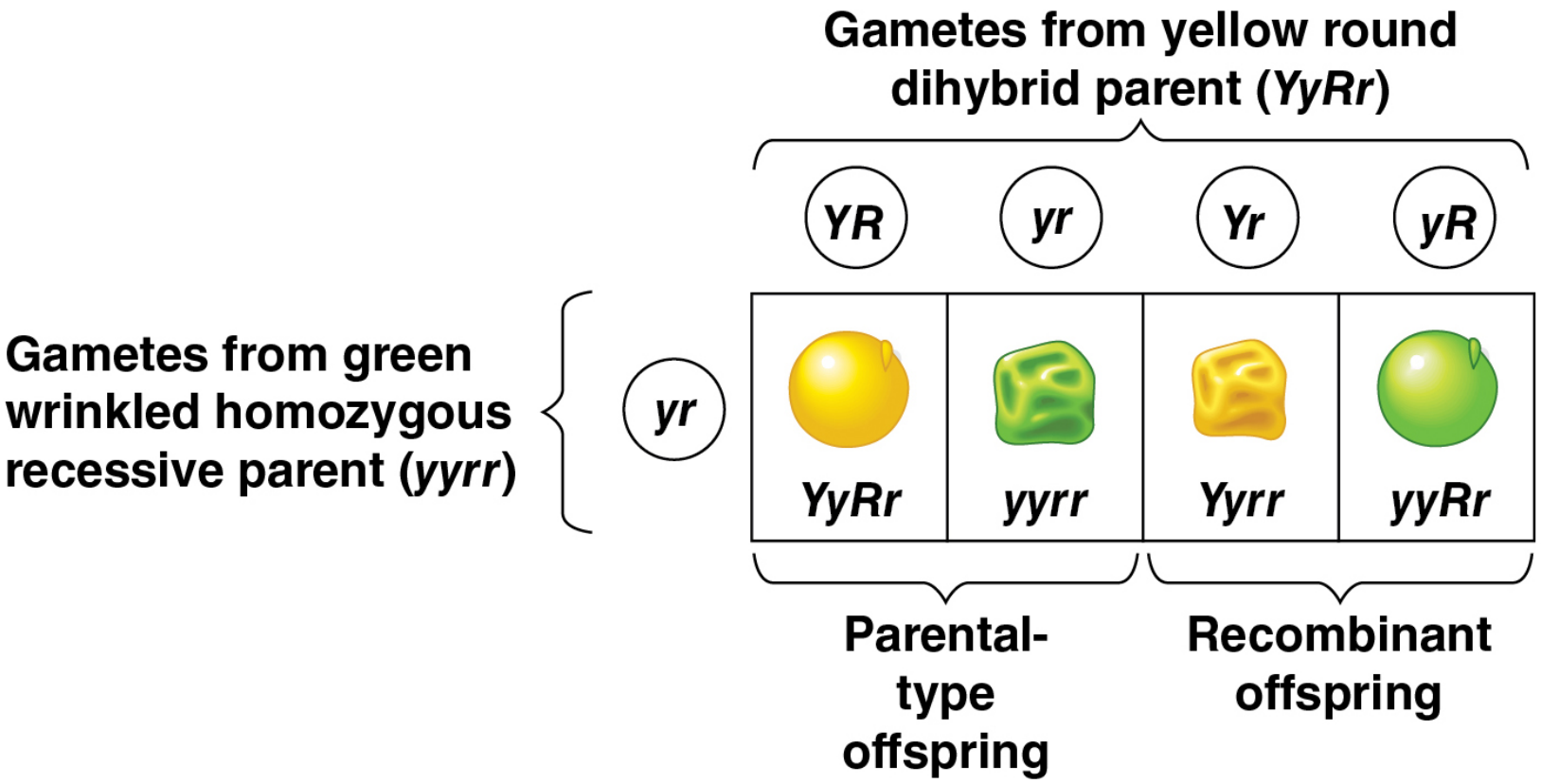
Genetic Recombination and Linkage

- The genetic findings of Mendel and Morgan relate to the chromosomal basis of recombination

Recombination of Unlinked Genes: Independent Assortment of Chromosomes

- Offspring with a phenotype matching one of the parental (P) phenotypes are called **parental types**
- Offspring with nonparental phenotypes (new combinations of traits) are called **recombinant types**, or **recombinants**
- A 50% frequency of recombination is observed for any two genes on different chromosomes

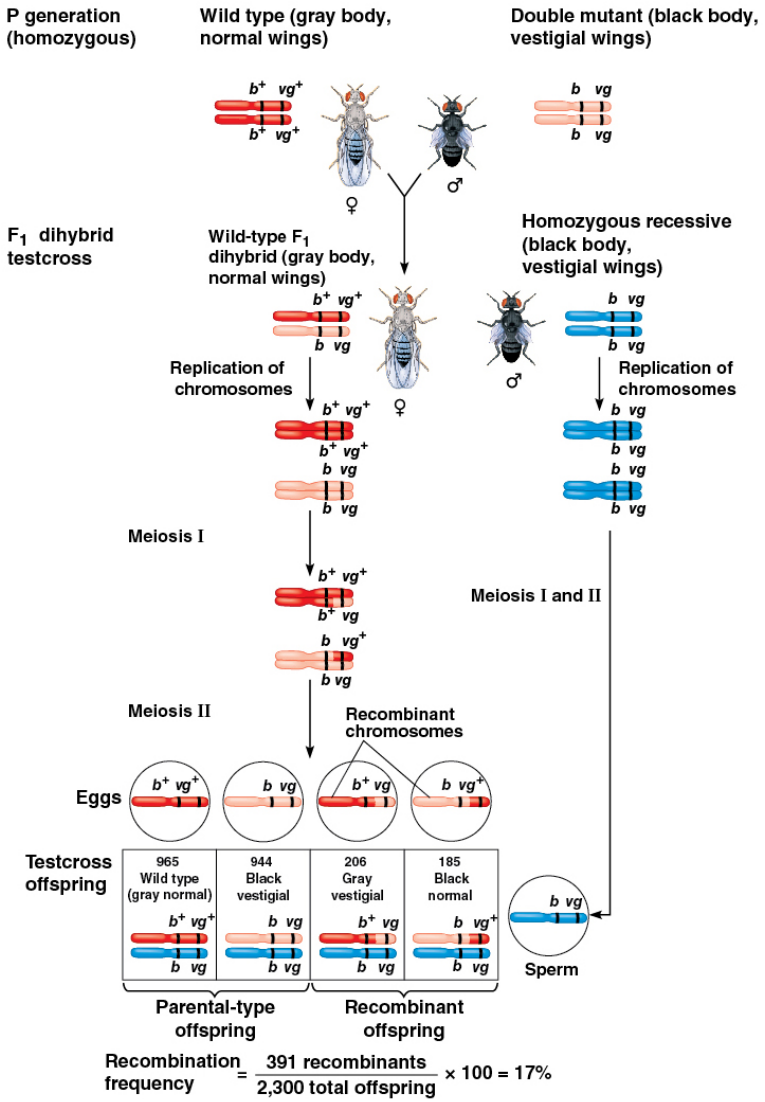
Figure 15.UN02



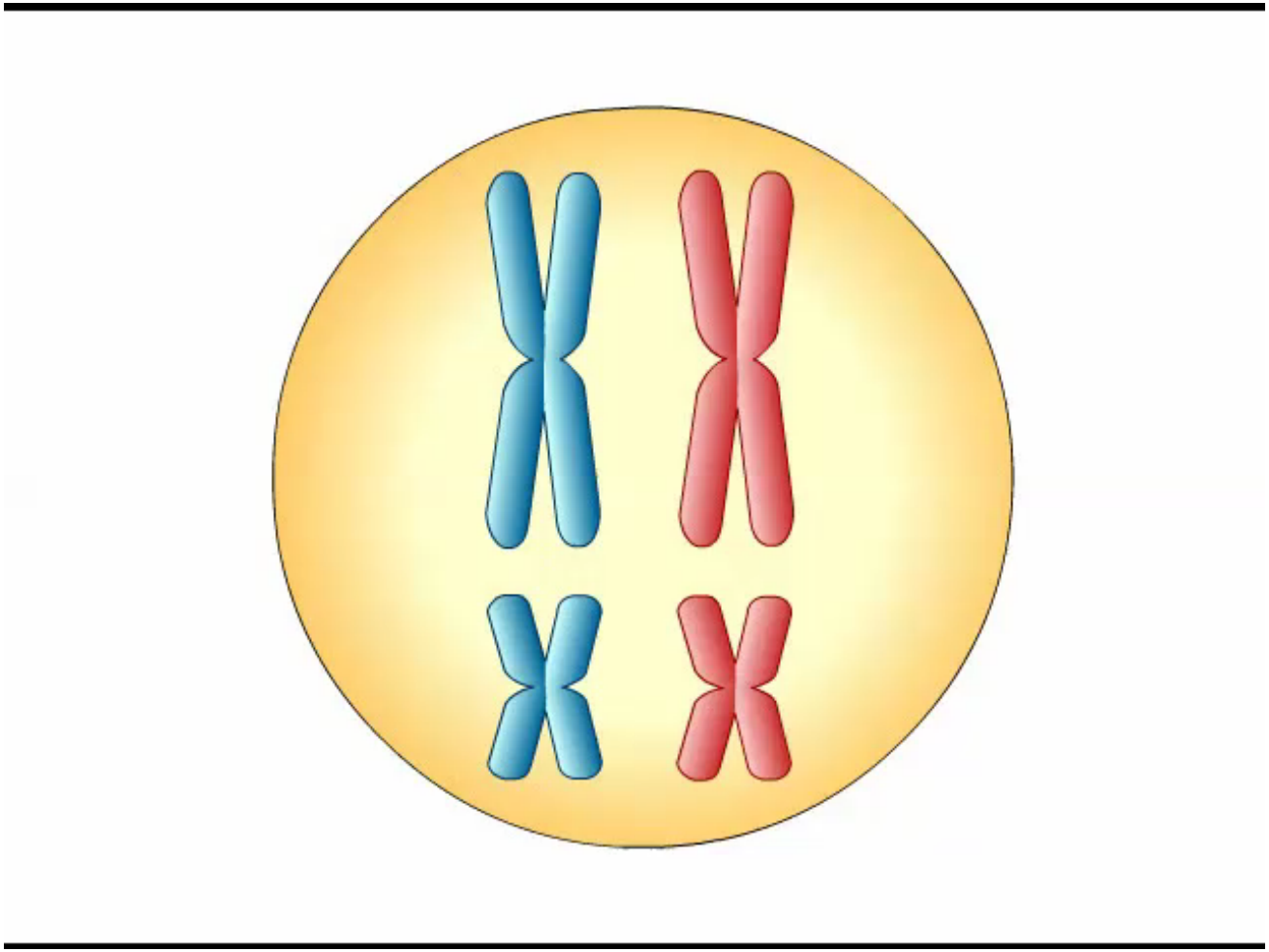
Recombination of Linked Genes: Crossing Over

- Morgan observed that although some genes are linked, nonparental allele combinations are still produced
- He proposed that some process must occasionally break the physical connection between genes on the same chromosome
- That mechanism was the **crossing over** of homologous chromosomes

Figure 15.10


P generation (homozygous)
Wild type (gray body, normal wings)
Double mutant (black body, vestigial wings)
b+ vg+
b vg
♀
♂
F1 dihybrid testcross
Wild-type F1 dihybrid (gray body, normal wings)
Homozygous recessive (black body, vestigial wings)
Replication of chromosomes
Meiosis I
Meiosis I and II
Meiosis II
Recombinant chromosomes
Eggs
Sperm
Testcross offspring
965 Wild type (gray normal)
944 Black vestigial
206 Gray vestigial
185 Black normal
Parental-type offspring
Recombinant offspring
Recombination frequency = 391 recombinants / 2,300 total offspring × 100 = 17%

Animation: Linked Genes and Crossing Over



New Combinations of Alleles: Variation for Natural Selection

- Recombinant chromosomes bring alleles together in new combinations in gametes
- Random fertilization increases even further the number of variant combinations that can be produced
- This abundance of genetic variation is the raw material upon which natural selection works

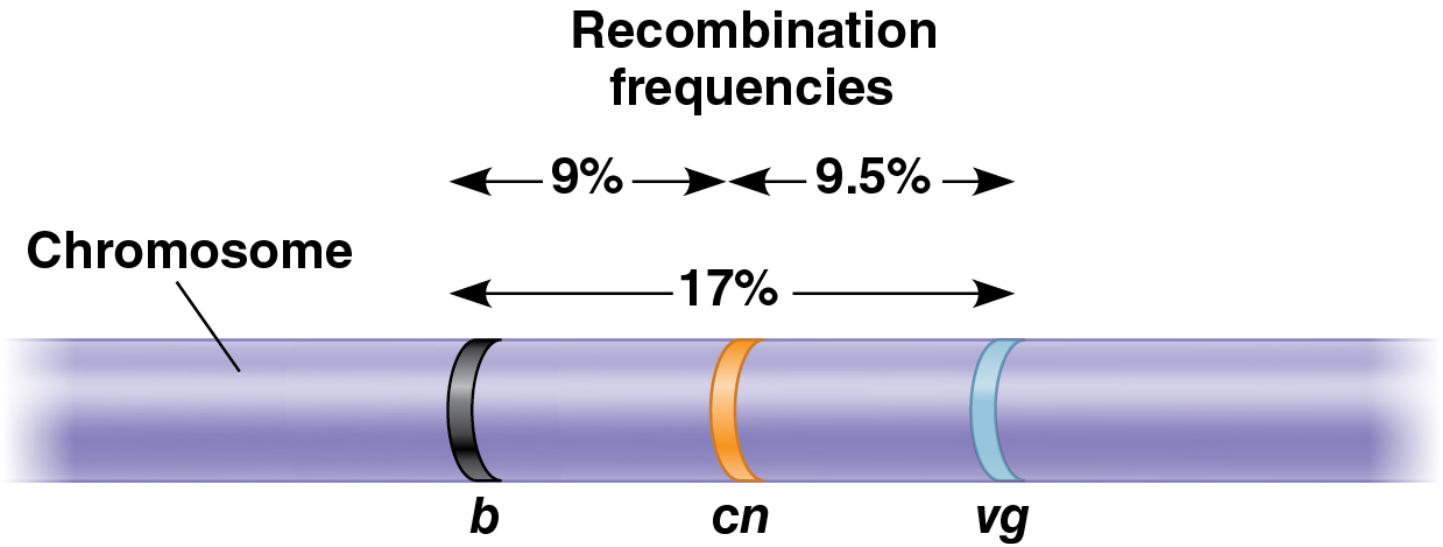
Mapping the Distance Between Genes Using Recombination Data: *Scientific Inquiry*

- Alfred Sturtevant, one of Morgan's students, constructed a **genetic map**, an ordered list of the genetic loci along a particular chromosome
- Sturtevant predicted that *the farther apart two genes are, the higher the probability that a crossover will occur between them and therefore the higher the recombination frequency*

- A **linkage map** is a genetic map of a chromosome based on recombination frequencies
- Distances between genes can be expressed as **map units**; one map unit represents a 1% recombination frequency
- Map units indicate relative distance and order, not precise locations of genes

Figure 15.11

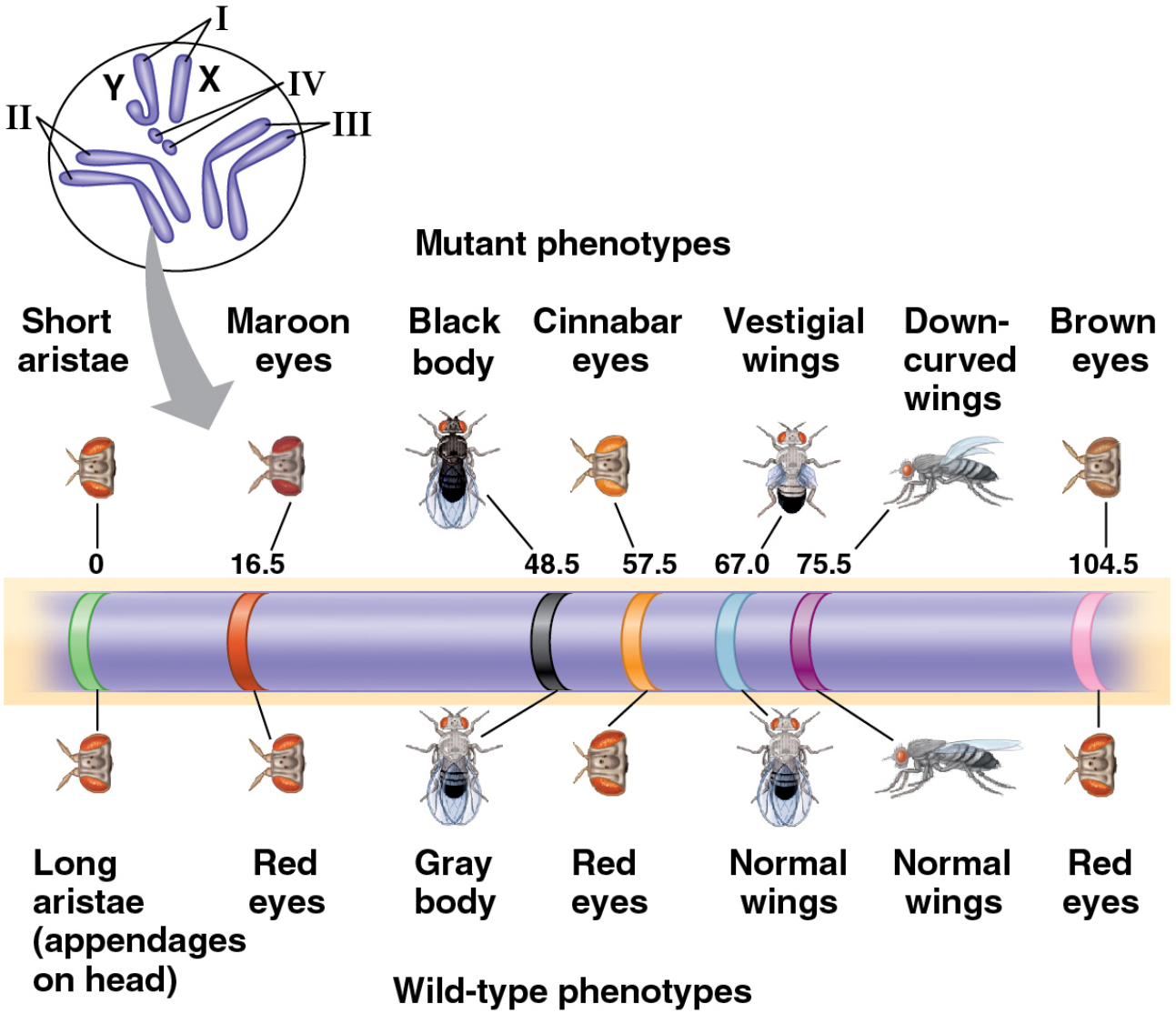
Results



- Genes that are far apart on the same chromosome can have a recombination frequency near 50%
- Such genes are physically linked, but genetically unlinked, and behave as if found on different chromosomes

- Sturtevant used recombination frequencies to make linkage maps of fruit fly genes
- They found that the genes clustered into four groups of linked genes (linkage groups)
- The linkage maps, combined with the fact that there are four chromosomes in *Drosophila*, provided additional evidence that genes are located on chromosomes

Figure 15.12


I
Y
X
IV
II
III
Mutant phenotypes
Short aristae
Maroon eyes
Black body
Cinnabar eyes
Vestigial wings
Down-curved wings
Brown eyes
0
16.5
48.5
57.5
67.0
75.5
104.5
Long aristae (appendages on head)
Red eyes
Gray body
Red eyes
Normal wings
Normal wings
Red eyes
Wild-type phenotypes

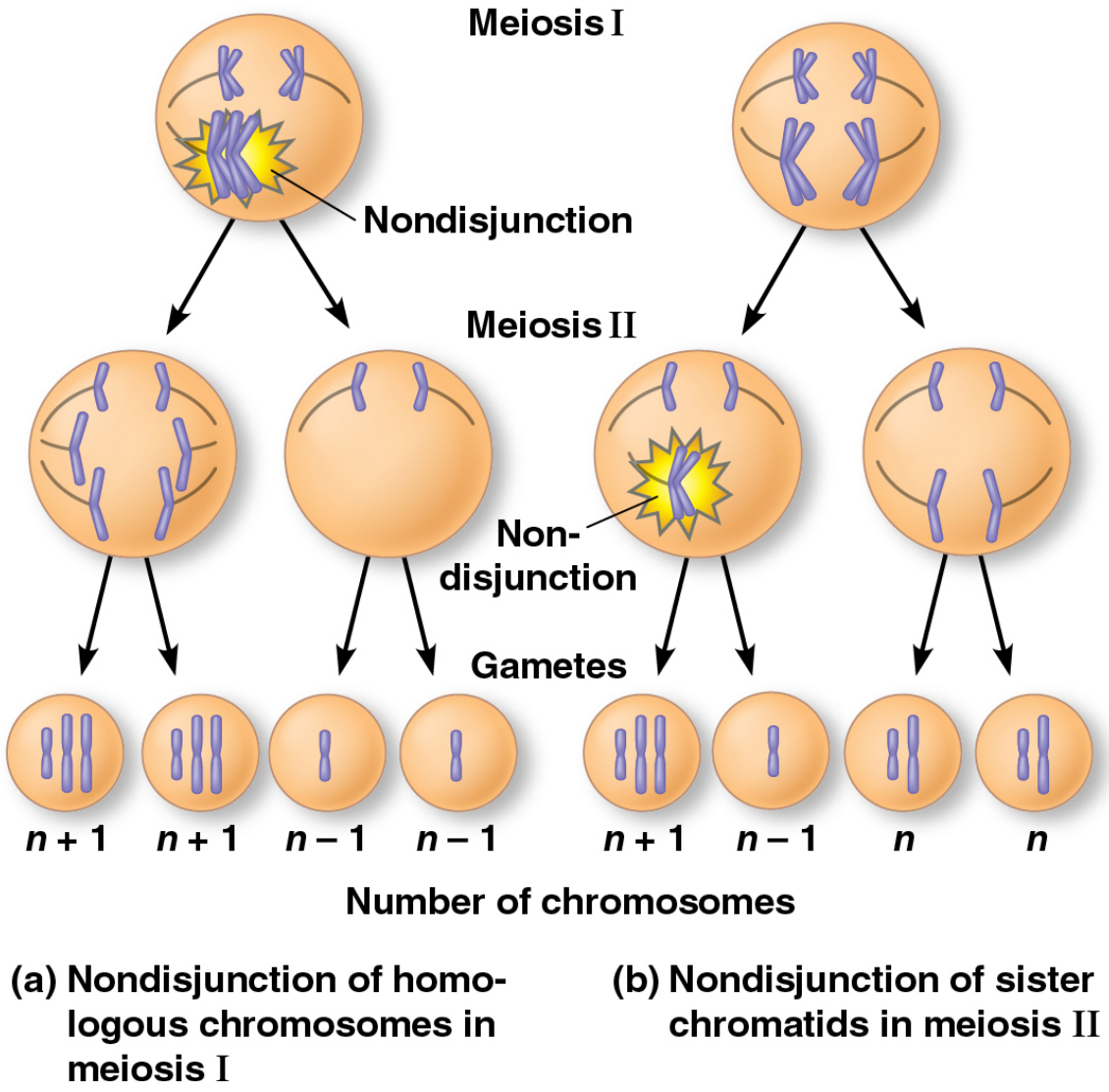
Concept 15.4: Alterations of chromosome number or structure cause some genetic disorders

- Large-scale chromosomal alterations in humans and other mammals often lead to spontaneous abortions (miscarriages) or cause a variety of developmental disorders
- Plants tolerate such genetic changes better than animals do

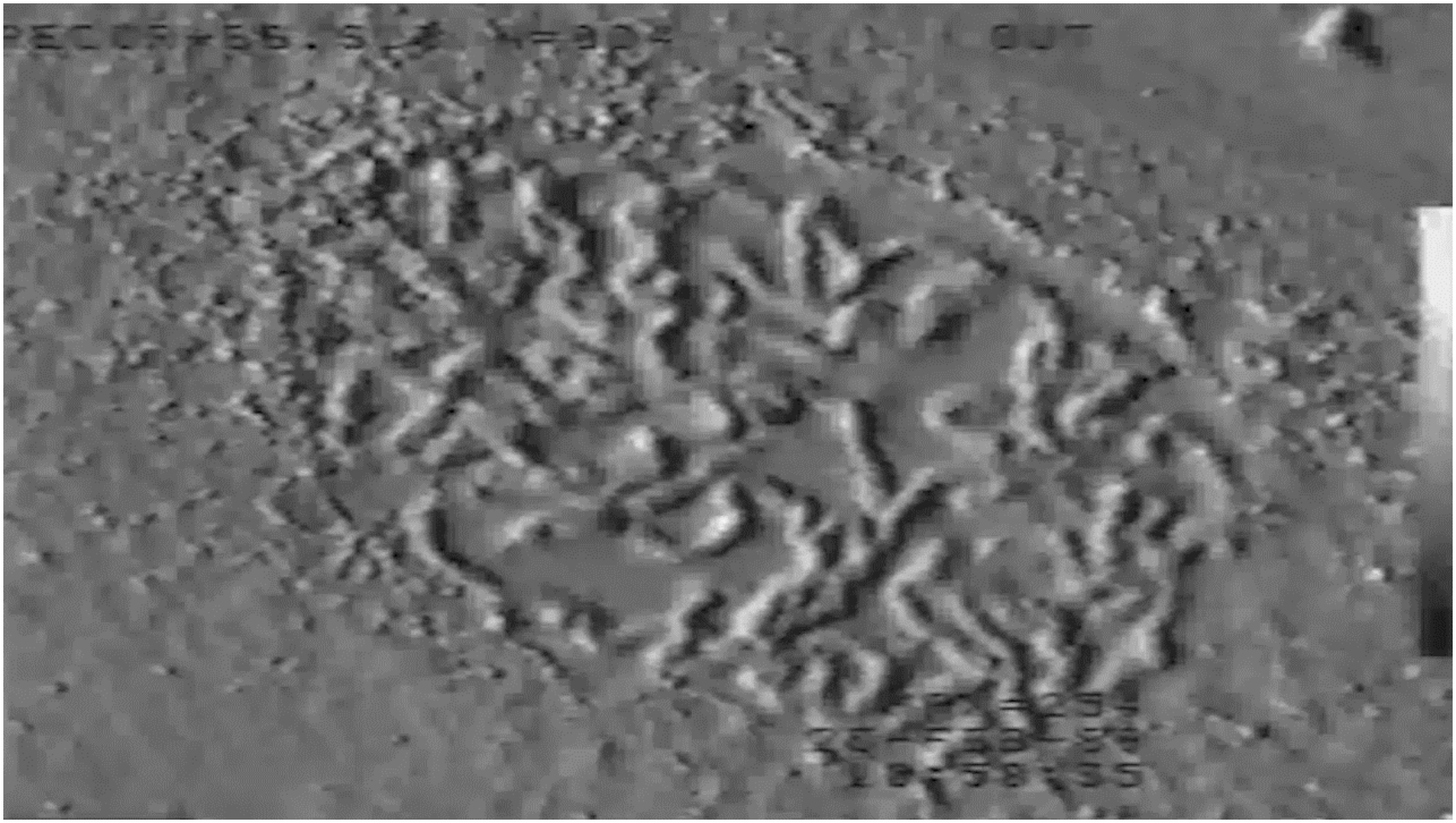
Abnormal Chromosome Number

- In **nondisjunction**, pairs of homologous chromosomes do not separate normally during meiosis
- As a result, one gamete receives two of the same type of chromosome, and another gamete receives no copy

Figure 15.13


Meiosis I
Nondisjunction
Meiosis II
Non-
disjunction
Gametes
n + 1
n + 1
n – 1
n – 1
n + 1
n – 1
n
n
Number of chromosomes
(a) Nondisjunction of homologous chromosomes in meiosis I
(b) Nondisjunction of sister chromatids in meiosis II

Video: Nondisjunction in Mitosis



- **Aneuploidy** results from the fertilization of gametes in which nondisjunction occurred
- Offspring with this condition have an abnormal number of a particular chromosome

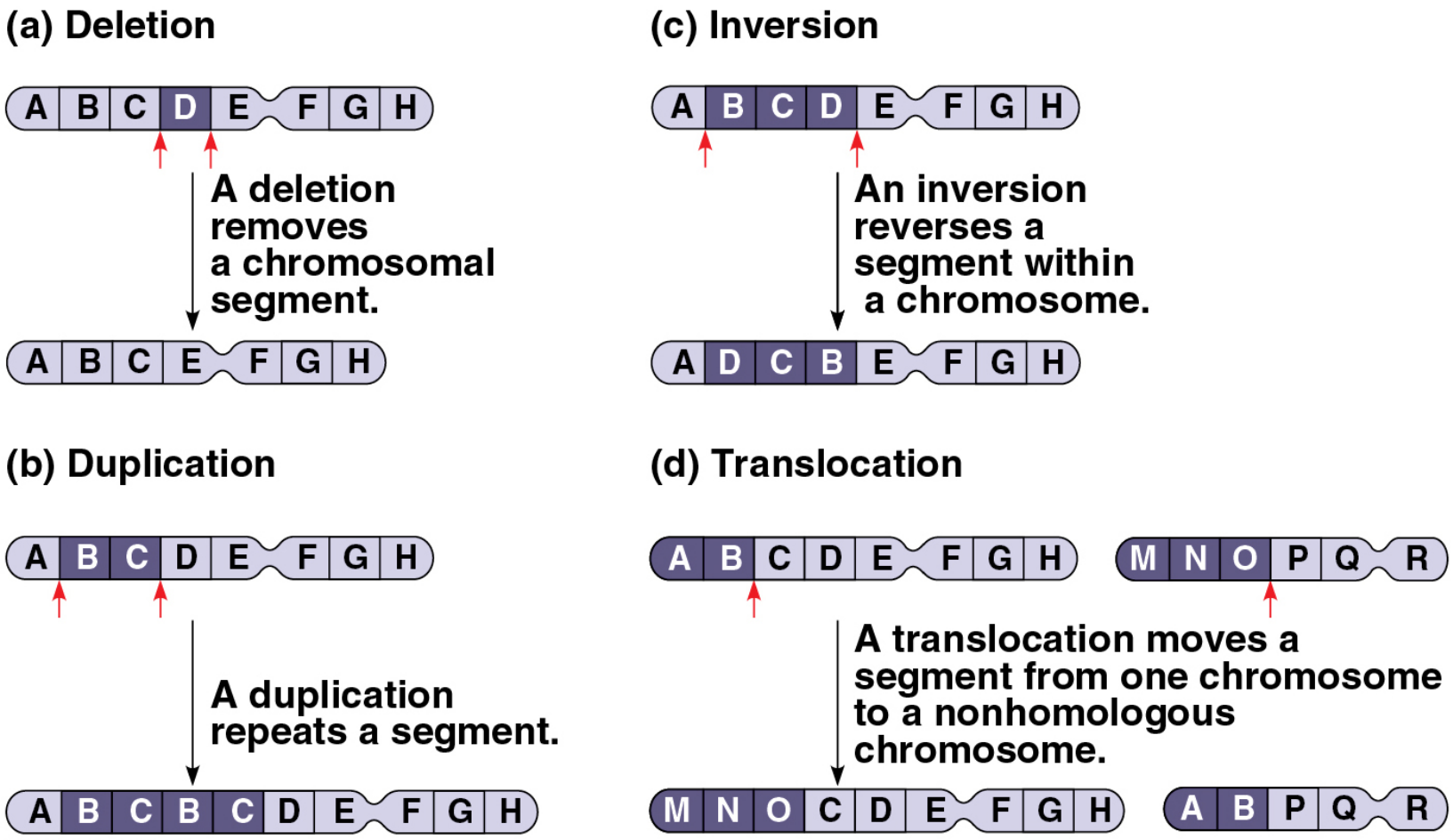
- A **monosomic** zygote has only one copy of a particular chromosome
- A **trisomic** zygote has three copies of a particular chromosome

- **Polyploidy** is a condition in which an organism has more than two complete sets of chromosomes
  - Triploidy (3*n*) is three sets of chromosomes
  - Tetraploidy (4*n*) is four sets of chromosomes
- Polyploidy is common in plants, but not animals
- Polyploids are more normal in appearance than aneuploids

Alterations of Chromosome Structure

- Breakage of a chromosome can lead to four types of changes in chromosome structure:
  - **Deletion** removes a chromosomal fragment
  - **Duplication** repeats a segment
  - **Inversion** reverses orientation of a segment within a chromosome
  - **Translocation** moves a segment from one chromosome to another

Figure 15.14


(a) Deletion
A B C D E F G H
A deletion removes a chromosomal segment.
A B C E F G H
(c) Inversion
A B C D E F G H
An inversion reverses a segment within a chromosome.
A D C B E F G H
(b) Duplication
A B C D E F G H
A duplication repeats a segment.
A B C B C D E F G H
(d) Translocation
A B C D E F G H
M N O P Q R
A translocation moves a segment from one chromosome to a nonhomologous chromosome.
M N O C D E F G H
A B P Q R

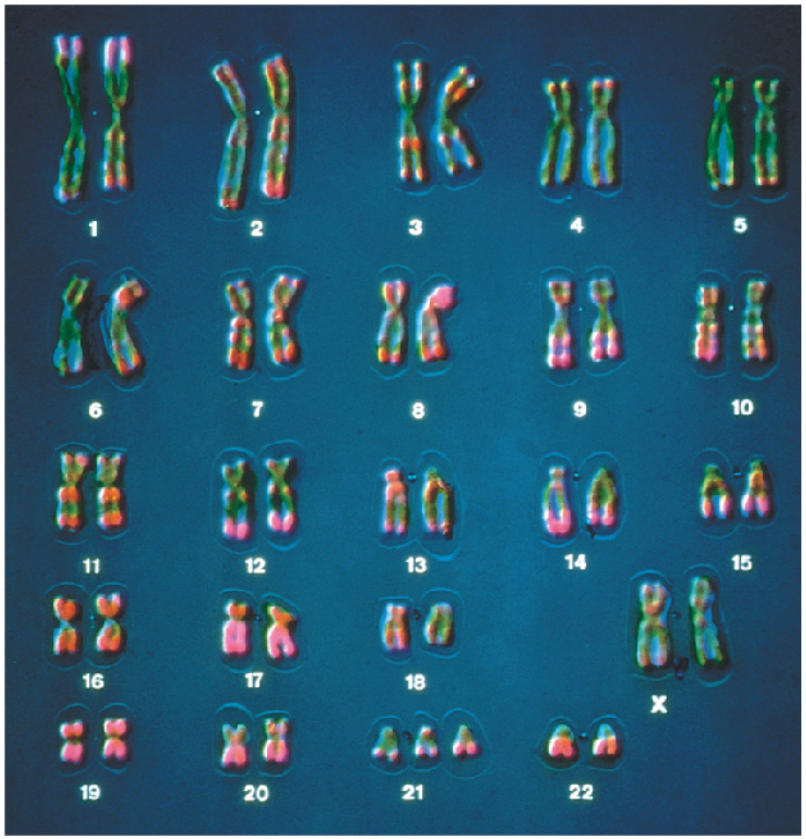
Human Disorders Due to Chromosomal Alterations

- Alterations of chromosome number and structure are associated with some serious disorders
- Some types of aneuploidy appear to upset the genetic balance less than others, resulting in individuals surviving to birth and beyond
- These surviving individuals have a set of symptoms, or syndrome, characteristic of the type of aneuploidy

Down Syndrome (Trisomy 21)

- **Down syndrome** is an aneuploid condition that results from three copies of chromosome 21
- It affects about one out of every 830 children born in the United States
- The frequency of Down syndrome increases with the age of the mother, a correlation that has not been explained

Figure 15.15



Aneuploidy of Sex Chromosomes

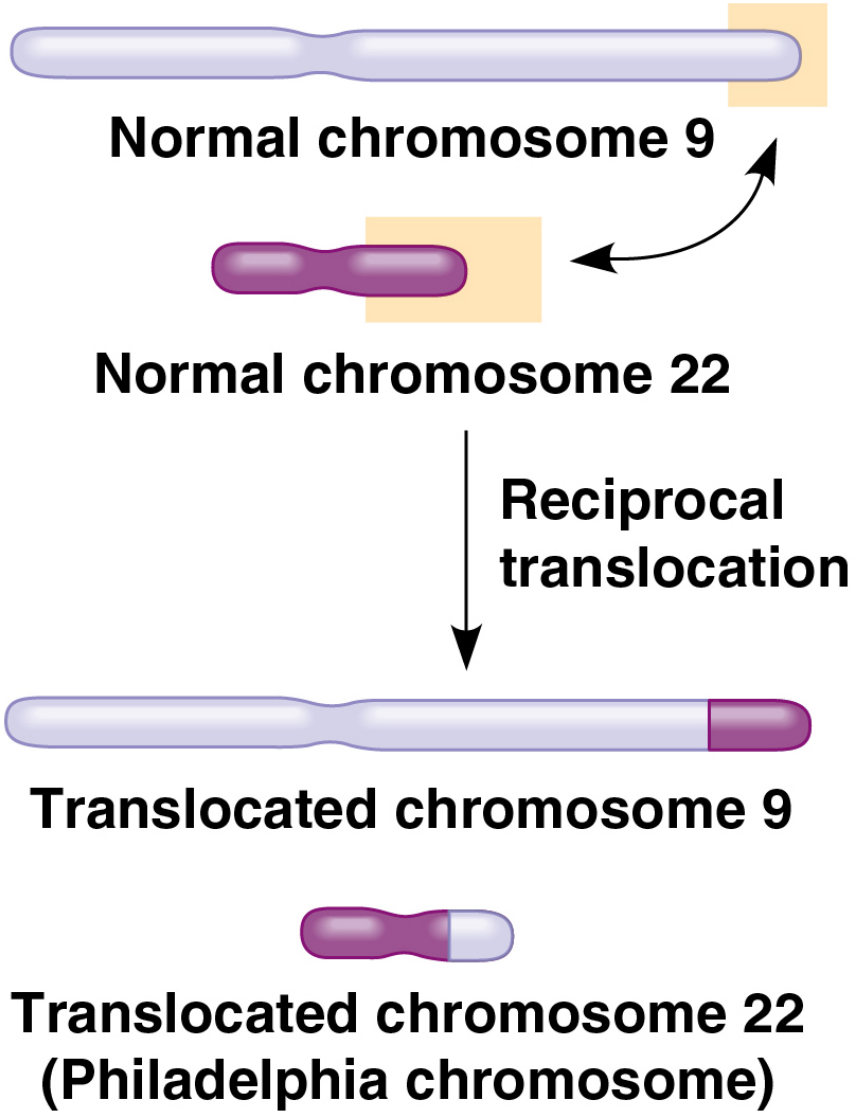
- Nondisjunction of sex chromosomes produces a variety of aneuploid conditions
- Klinefelter syndrome is the result of an extra chromosome in a male, producing XXY individuals
- About one in 1,000 males is XYY; these males do not exhibit any syndrome

- XXX females occur with a frequency of about one in 1,000
- They are healthy, with no unusual physical features, though they are at risk for learning disabilities
- Monosomy X, called *Turner syndrome*, produces X0 females, who are sterile; it is the only known viable monosomy in humans

Disorders Caused by Structurally Altered Chromosomes

- The syndrome *cri du chat* (“cry of the cat”), results from a specific deletion in chromosome 5
- A child born with this syndrome is severely intellectually disabled and has a catlike cry; individuals usually die in infancy or early childhood
- Certain cancers, including *chronic myelogenous leukemia (CML)*, are caused by translocations of chromosomes

Figure 15.16


Normal chromosome 9
Normal chromosome 22
Reciprocal translocation
Translocated chromosome 9
Translocated chromosome 22 (Philadelphia chromosome)

Concept 15.5: Some inheritance patterns are exceptions to standard Mendelian inheritance

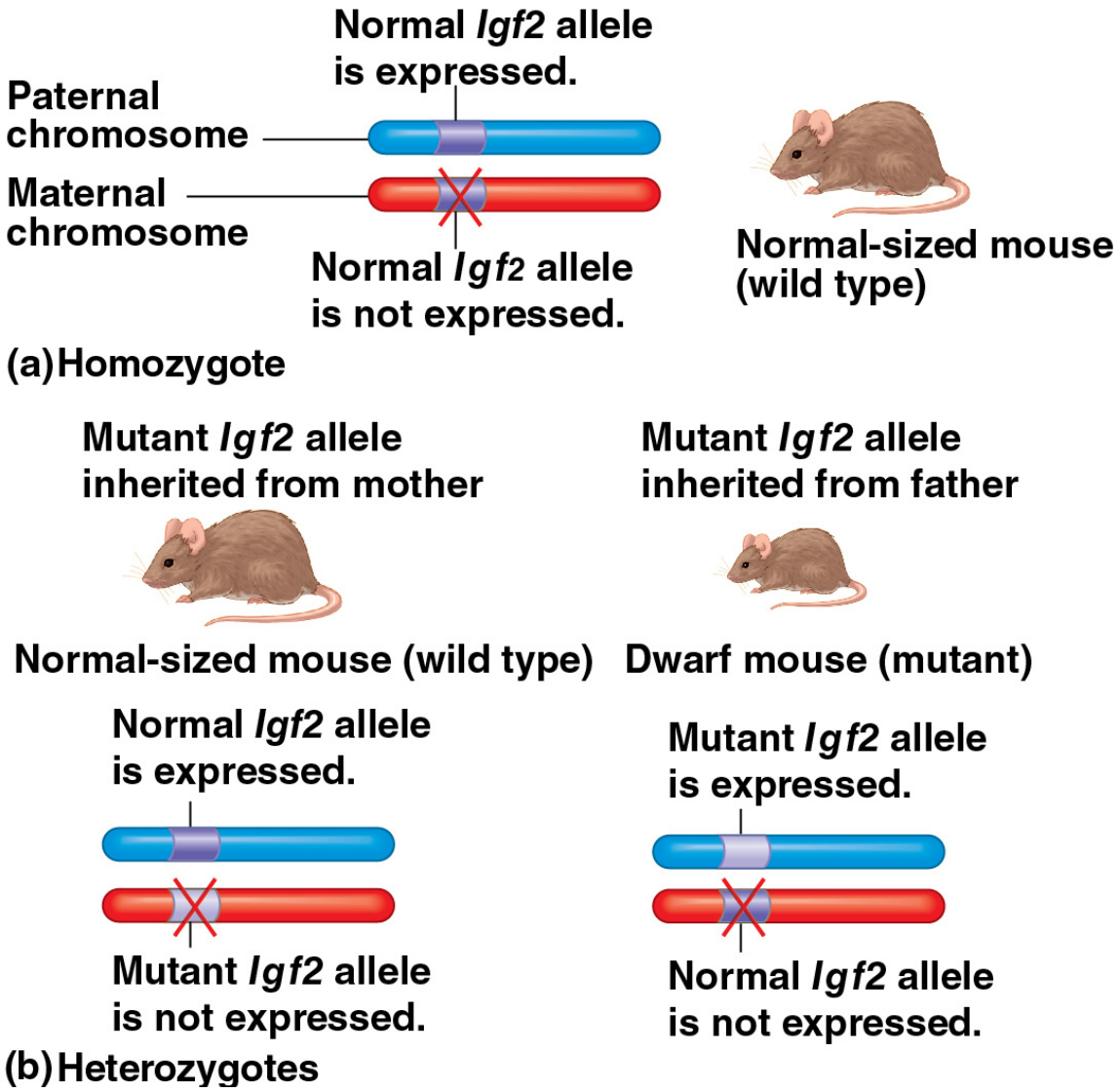
- There are two normally occurring exceptions to Mendelian genetics
- One exception involves genes located in the nucleus, and the other involves genes located outside the nucleus
- In both cases, the sex of the parent contributing an allele is a factor in the pattern of inheritance

Genomic Imprinting

- For a few mammalian traits, the phenotype depends on which parent passed along the alleles for those traits
- Such variation in phenotype is called **genomic imprinting**
- Genomic imprinting involves the silencing of certain genes depending on which parent passes them on
- Most imprinted genes are on autosomes

- The mouse gene for insulin-like growth factor 2 (*Igf2*) was one of the first imprinted genes to be identified
- Only the paternal allele of this gene is expressed

Figure 15.17

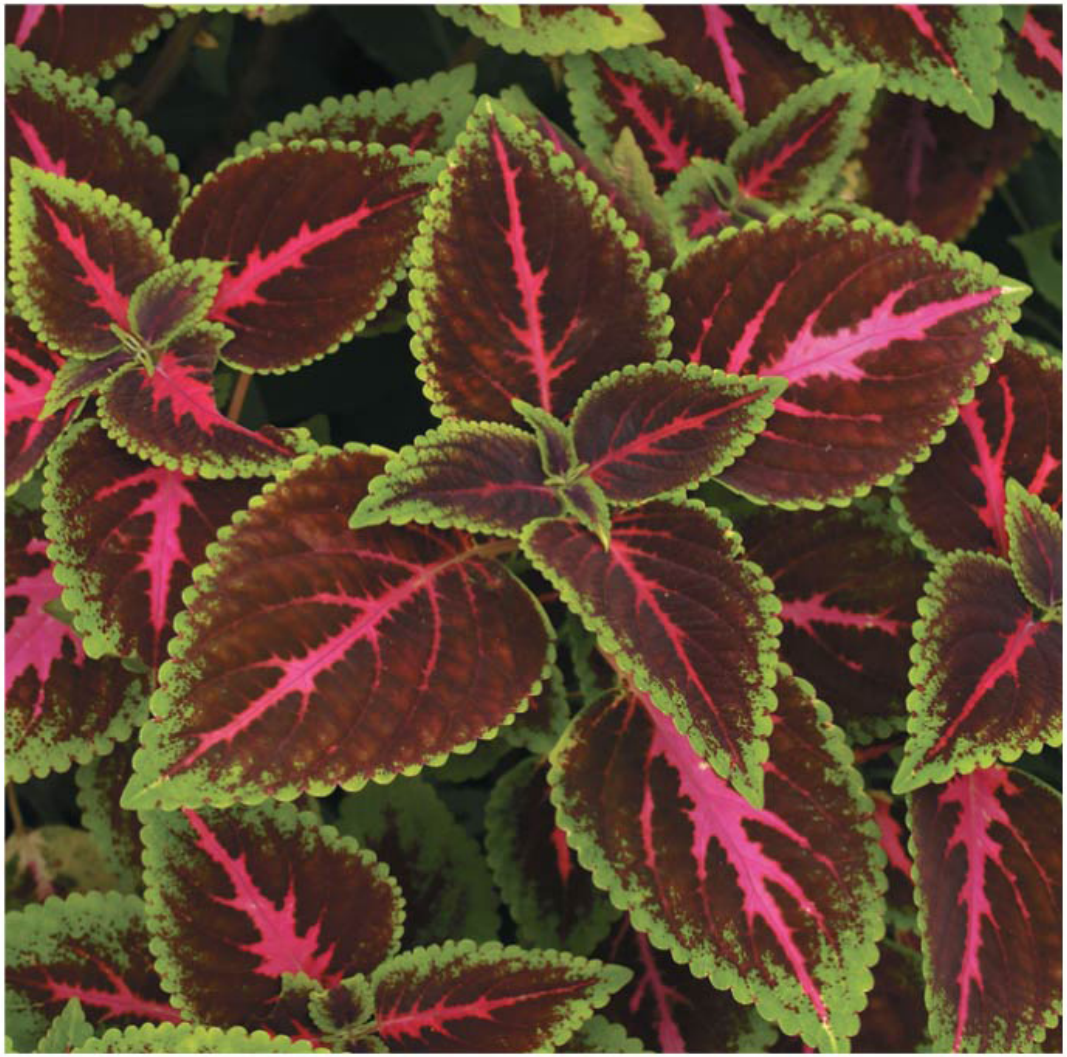

Normal *Igf2* allele is expressed.
Paternal chromosome
Maternal chromosome
Normal *Igf2* allele is not expressed.
Normal-sized mouse (wild type)
(a) Homozygote
Mutant *Igf2* allele inherited from mother
Mutant *Igf2* allele inherited from father
Normal-sized mouse (wild type)
Dwarf mouse (mutant)
Normal *Igf2* allele is expressed.
Mutant *Igf2* allele is not expressed.
Mutant *Igf2* allele is expressed.
Normal *Igf2* allele is not expressed.
(b) Heterozygotes

- It seems that imprinting is the result of the methylation (addition of —CH_3 groups) of cysteine nucleotides
- Genomic imprinting may affect only a small fraction of mammalian genes
- Most imprinted genes are critical for embryonic development

Inheritance of Organelle Genes

- Extranuclear genes (or cytoplasmic genes) are found in organelles in the cytoplasm
- Mitochondria, as well as chloroplasts, and other plant plastids carry small circular DNA molecules
- Extranuclear genes are inherited maternally because the zygote's cytoplasm comes from the egg
- The first evidence of extranuclear genes came from studies on the inheritance of yellow or white patches on leaves of an otherwise green plant

Figure 15.18



- Some defects in mitochondrial genes prevent cells from making enough ATP and result in diseases that affect the muscular and nervous systems
  - For example, *mitochondrial myopathy* and *Leber's hereditary optic neuropathy*

- It may be possible to avoid passing along mitochondrial disorders
- The chromosomes from the egg of an affected mother could be transferred to an egg of a healthy donor, generating a “two-mother” egg
- This egg could then be fertilized by sperm from the prospective father and transplanted to the womb of the prospective mother

Figure 15.UN01a

Offspring from testcross of *AaBb* (F_1) × *aabb*	Purple stem/short petals (*A–B–*)	Green stem/short petals (*aaB–*)	Purple stem/long petals (*A–bb*)	Green stem/long petals (*aabb*)
Expected ratio if the genes are unlinked	1	1	1	1
Expected number of offspring (of 900)				
Observed number of offspring (of 900)	220	210	231	239

Figure 15.UN01b

Testcross Offspring	Expected (e)	Observed (o)	Deviation ($o - e$)	$(o - e)^2$	$(o - e)^2/e$
A–B–		220			
aaB–		210			
A–bb		231			
aabb		239			
				χ^2 = Sum	

Figure 15.UN01c

Cosmos plants

Figure 15.UN02

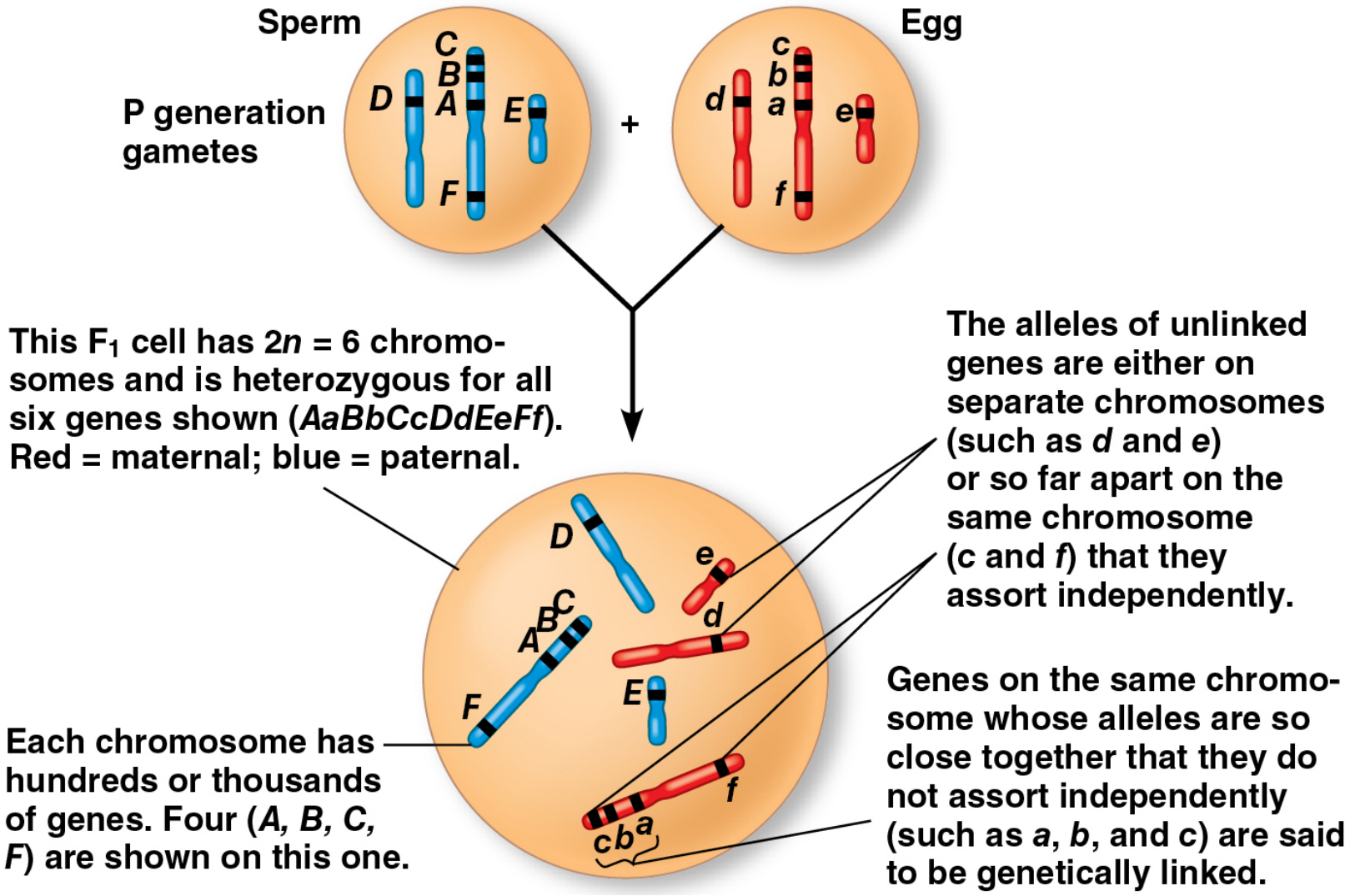


Figure 15.UN03