# Nature and consequences of altered chromosomal structure

# Introduction

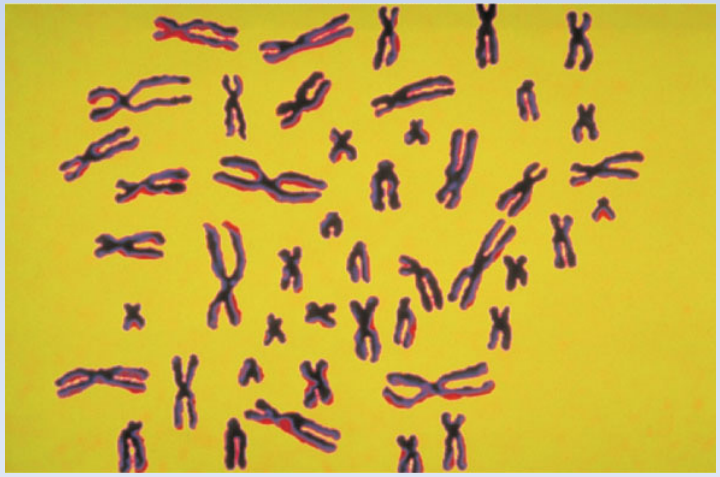
- Normal human cells contain 23 pairs of chromosomes
- This includes  one pair of sex chromosome XX or XY
- During cell division we can identify chromosomes
- Haploid: set of 23 chromosomes
- Diploid:  normal number of 46 chromosomes
- Aneuploidy: is either one extra or one less than normal chromosome. Usually is 45 or 47 and rarely 48,49
- Triploidy: 69 chromosomes

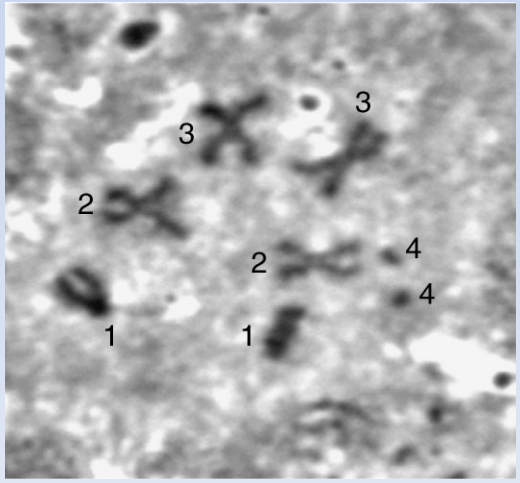
# GENETIC VARIATION

- Genetic variation
  - Includes genetic differences between members of the same species
    - Due to alterations of the genetic material
      - "Mutations"
  - Also includes genetic variation between members of different species
- Sources of genetic variation
  - Single gene mutations
    - Small changes occurring within a particular gene
  - Chromosome mutations
    - "Chromosomal aberrations"
    - Substantial change in chromosome structure
  - Genome mutations
    - Change in chromosome number

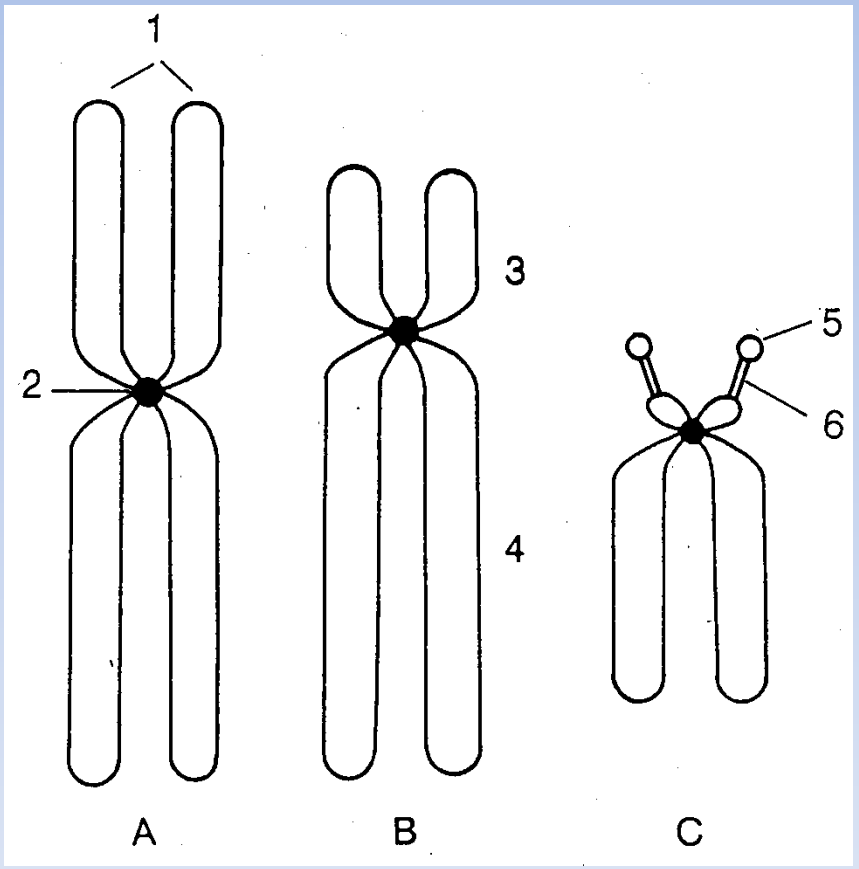
# CHROMOSOME STRUCTURE

- The composition of a chromosome can be changed
  - Can have major phenotypic effects on the organism
    - Cause of several genetic diseases
  - May appear normal, but have a high likelihood of producing offspring with genetic abnormalities
  - Important force in the evolution of new species





# Shapes of chromosomes

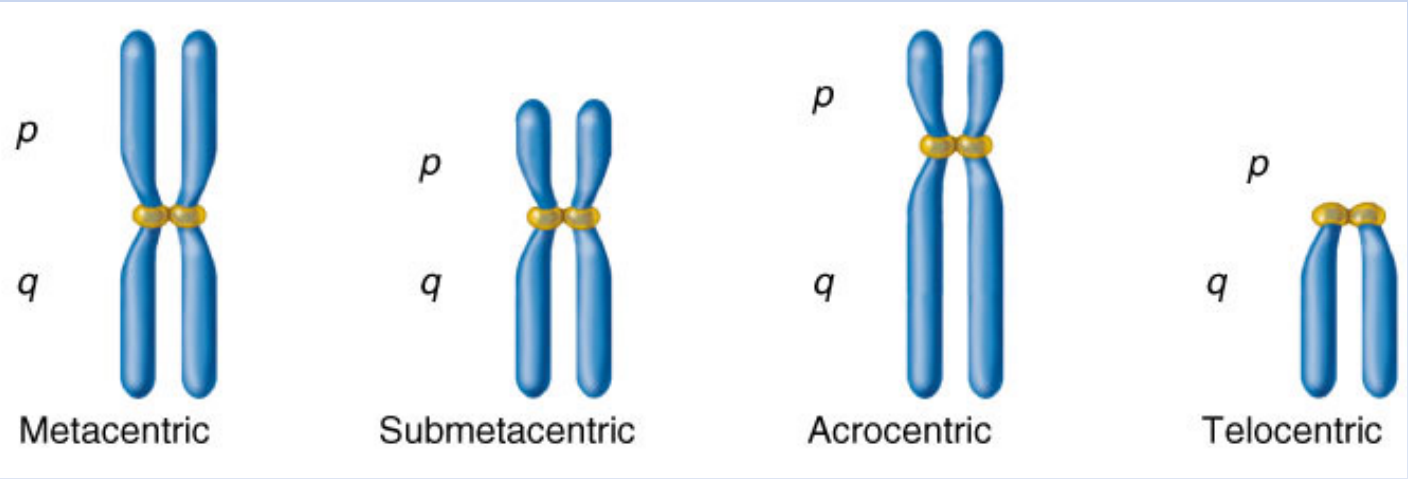



1: sister chromatids,
2: centromere,
3: short arm,
4: long arm,
5: satellite,
6: secondary constriction

A: metacentric, B: submetacentric, C: acrocentric

# CHROMOSOME STRUCTURE

- Chromosomes can vary considerably in size and shape
  - Various features used for identification
    - Size, Centromere location, Banding patterns
- Centromere location differs between chromosomes
  - At the middle in a **metacentric** chromosome
  - Near the middle in a **submetacentric** chromosome
  - Near an end in an **acrocentric** chromosome
  - At an end in a **telocentric** chromosome



# Mutations Can Alter Chromosome Structure

- There are two primary ways in which the structure of chromosomes can be altered
  - 1. The total amount of genetic information in the chromosome can change
    - Deficiencies/Deletions
    - Duplications
  - 2. The genetic material remains the same, but is rearranged
    - Inversions
    - Translocations

# Variation In Chromosome Structure

- Deficiency (or deletion)
  - The loss of a chromosomal segment
- Duplication
  - The repetition of a chromosomal segment compared to the normal parent chromosome
- Inversion
  - A change in the direction of the genetic material along a single chromosome
- Translocation
  - A segment of one chromosome becomes attached to a different chromosome
  - Simple translocations
    - One way transfer
  - Reciprocal translocations
    - Two way transfer

# Types of Chromosome Mutations

- Chromosome mutations can be grouped into three basic categories:

**Chromosome rearrangements**

alter the structure of chromosomes; for example, a piece of a chromosome might be duplicated, deleted, or inverted

**Aneuploids**

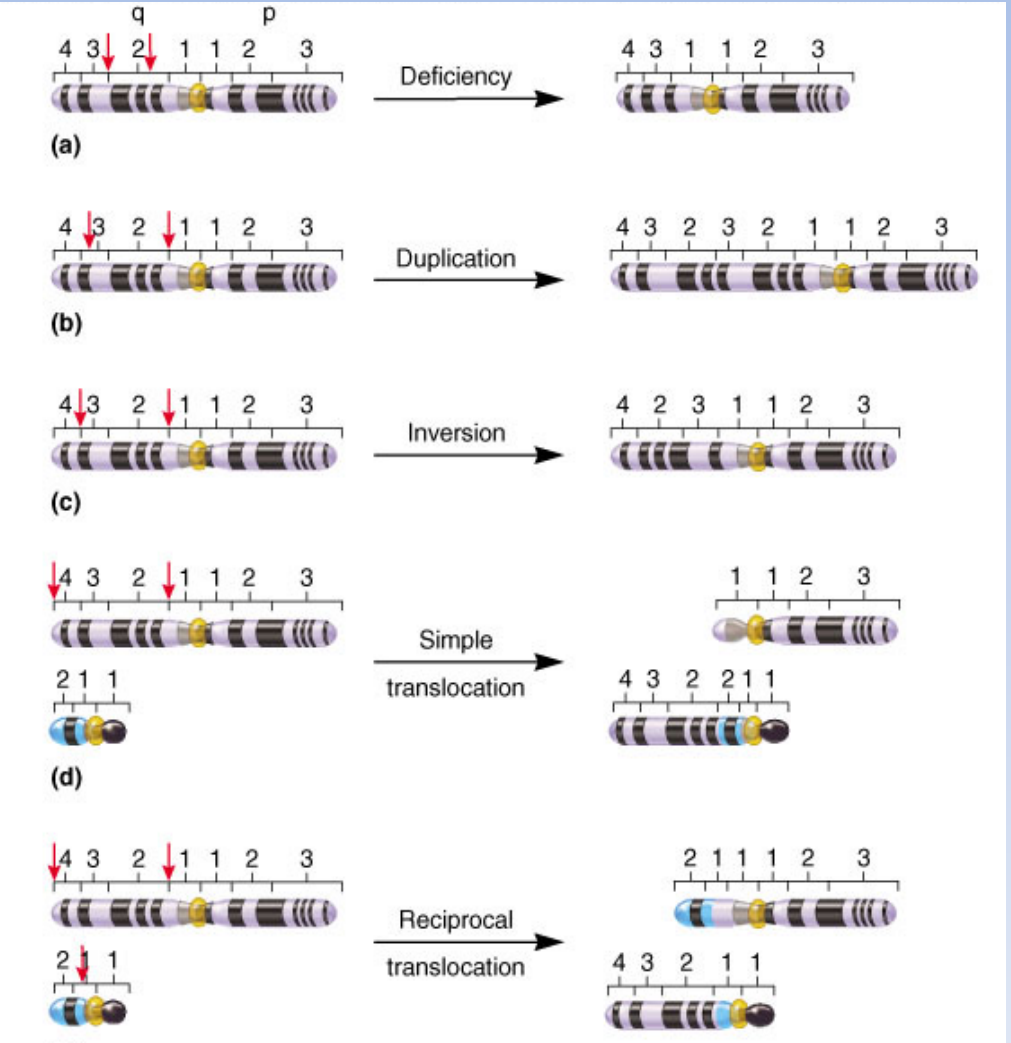
the *number* of chromosomes is altered: one or more individual chromosomes are added or deleted.

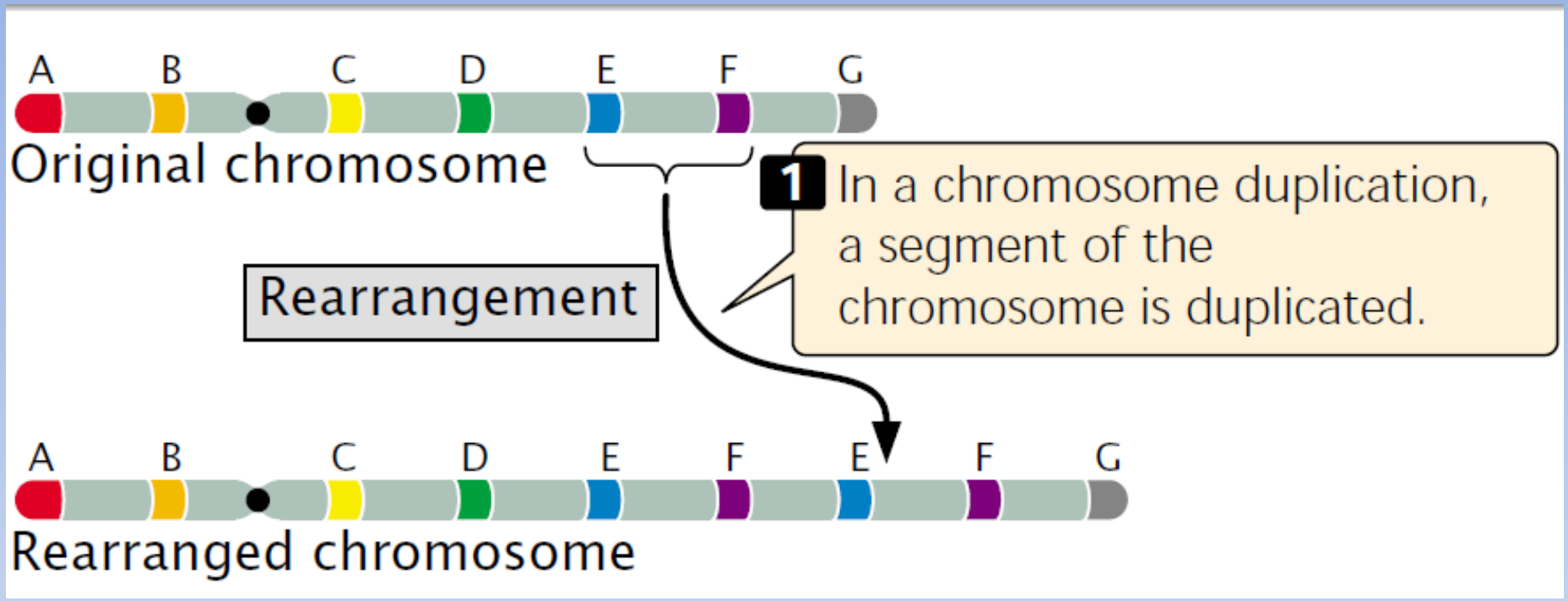
**Polyploids**

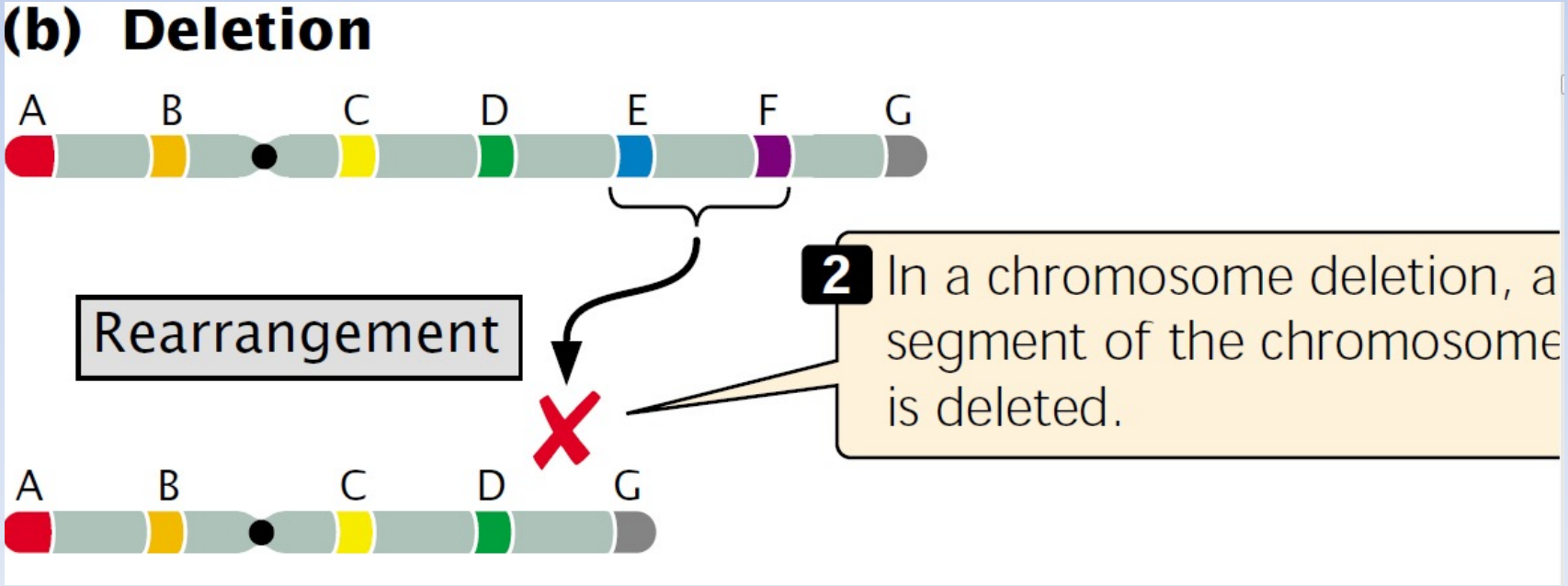
One or more complete sets of chromosomes are added. Some organisms (such as yeast) possess a single chromosome set (1n) for most of their life cycles and are referred to as haploid, whereas others possess two chromosome sets and are referred to as diploid (2n). A polyploid is any organism that has more than two sets of chromosomes (3n, 4n, 5n, or more).

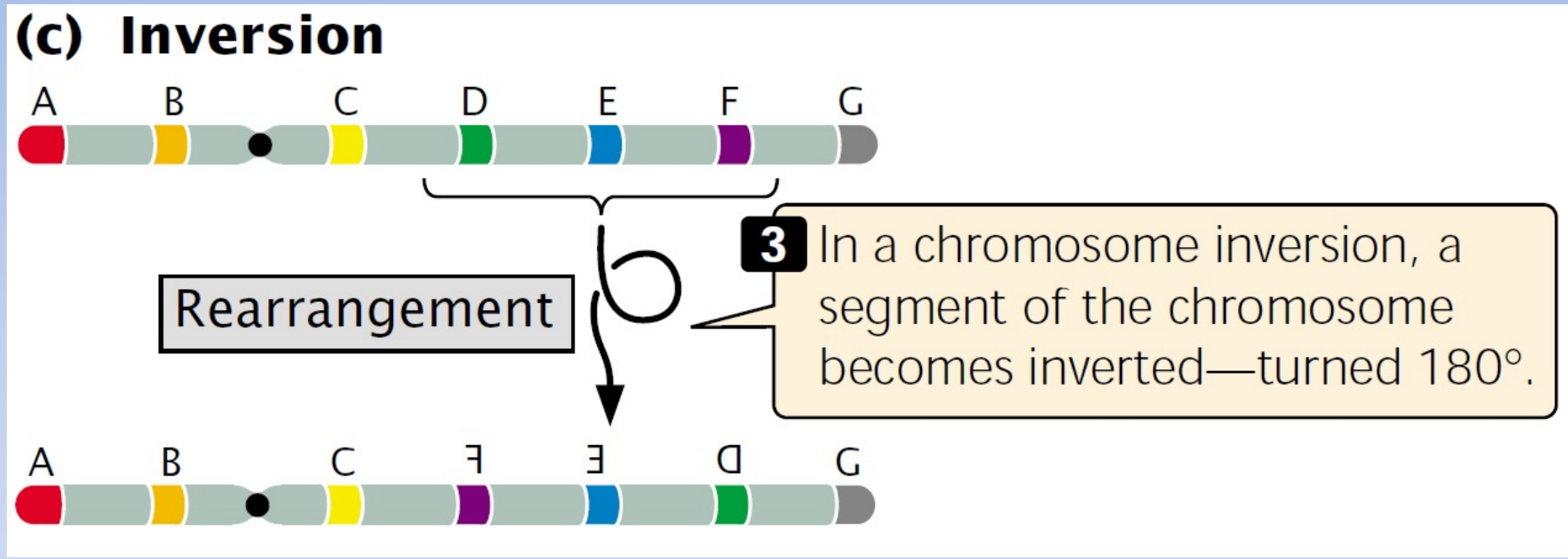
# Chromosome Rearrangements

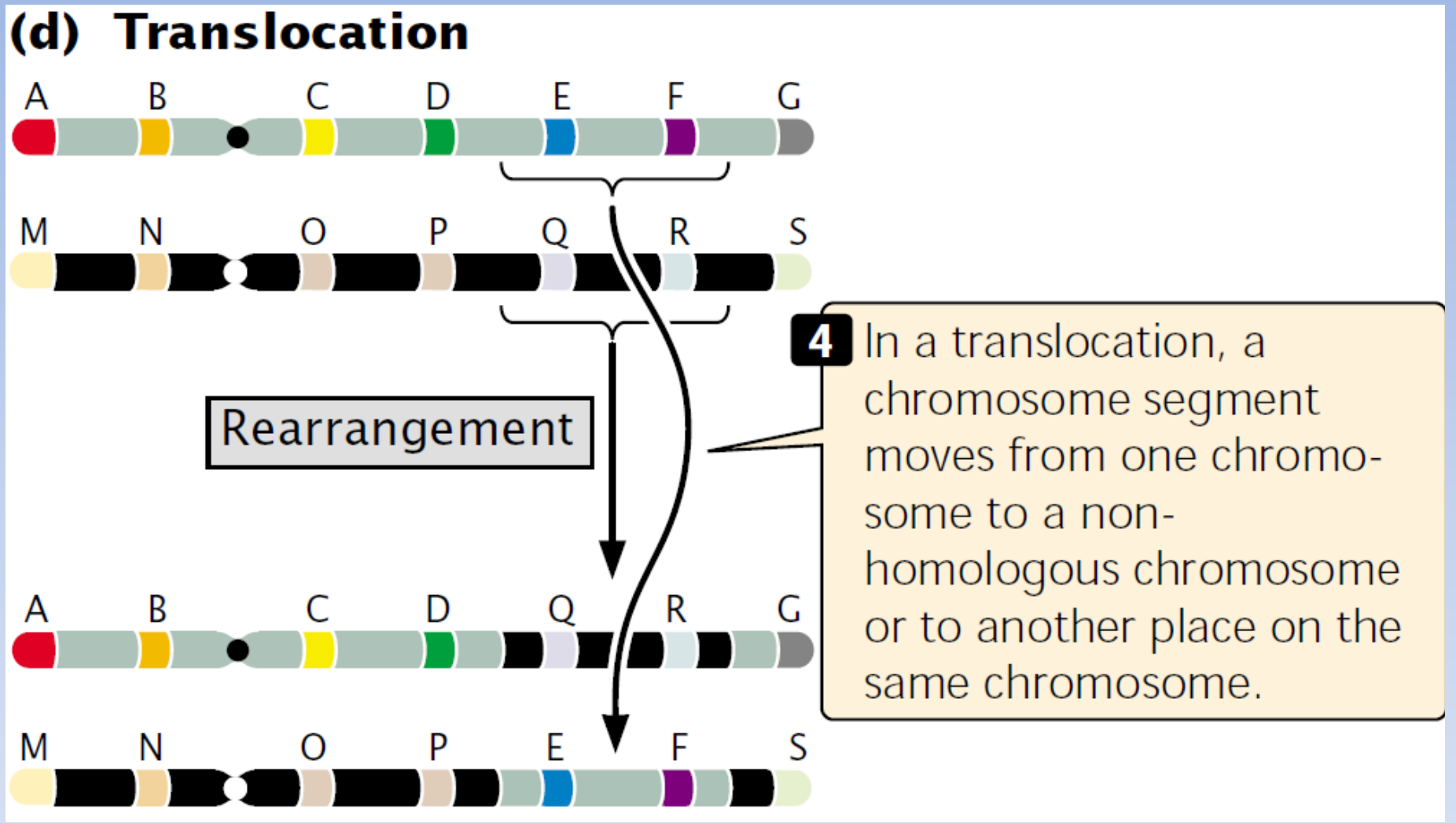
- Chromosome rearrangements are mutations that change the structure of individual chromosomes.
- The four basic types of rearrangements are
- Duplications,
- Deletions,
- Inversions,
- Translocations




A B C D E F G
Original chromosome
Rearrangement
1 In a chromosome duplication, a segment of the chromosome is duplicated.
A B C D E F E F G
Rearranged chromosome


(b) Deletion
A B C D E F G
Rearrangement
2 In a chromosome deletion, a segment of the chromosome is deleted.
A B C D G


(c) Inversion
A
B
C
D
E
F
G
Rearrangement
3 In a chromosome inversion, a segment of the chromosome becomes inverted—turned 180°.
A
B
C
F
E
D
G


(d) Translocation
A B C D E F G
M N O P Q R S
Rearrangement
A B C D Q R G
M N O P E F S
4 In a translocation, a chromosome segment moves from one chromo-some to a non-homologous chromosome or to another place on the same chromosome.

# **chromosome** Duplications

in which the duplicated region is immediately adjacent to the original segment, is called a

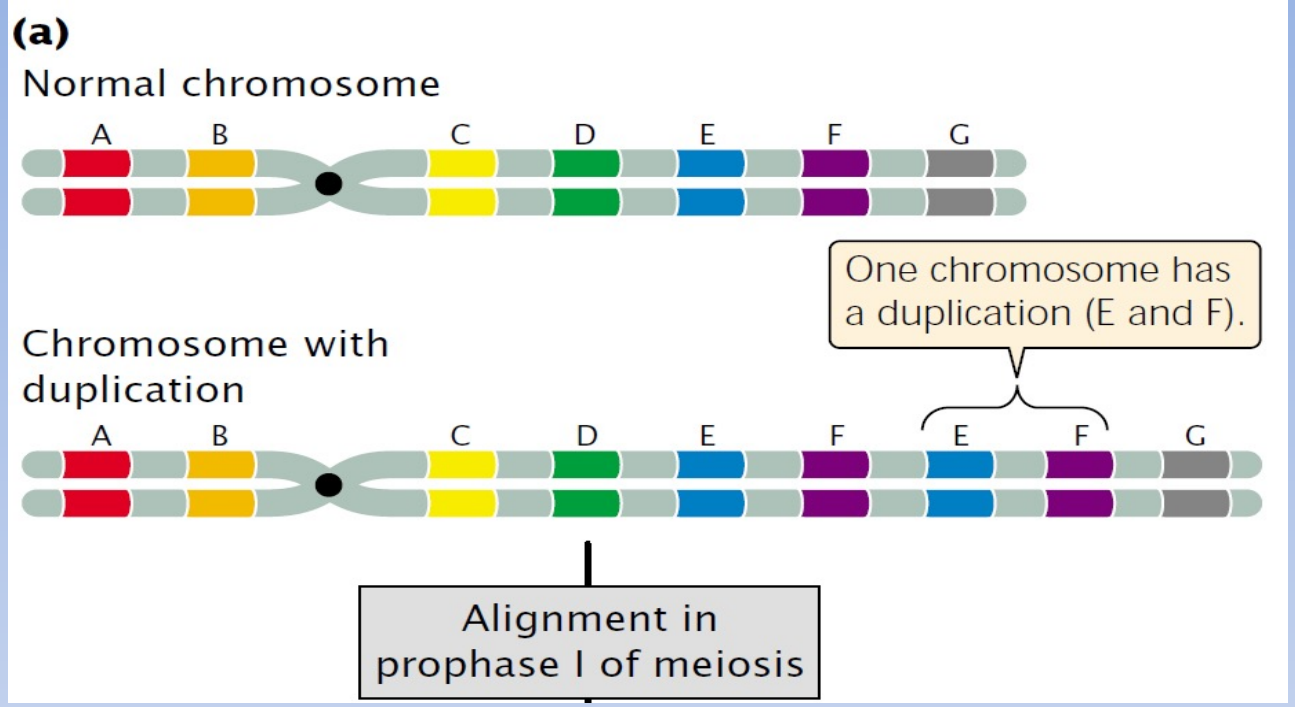
**tandem duplication**

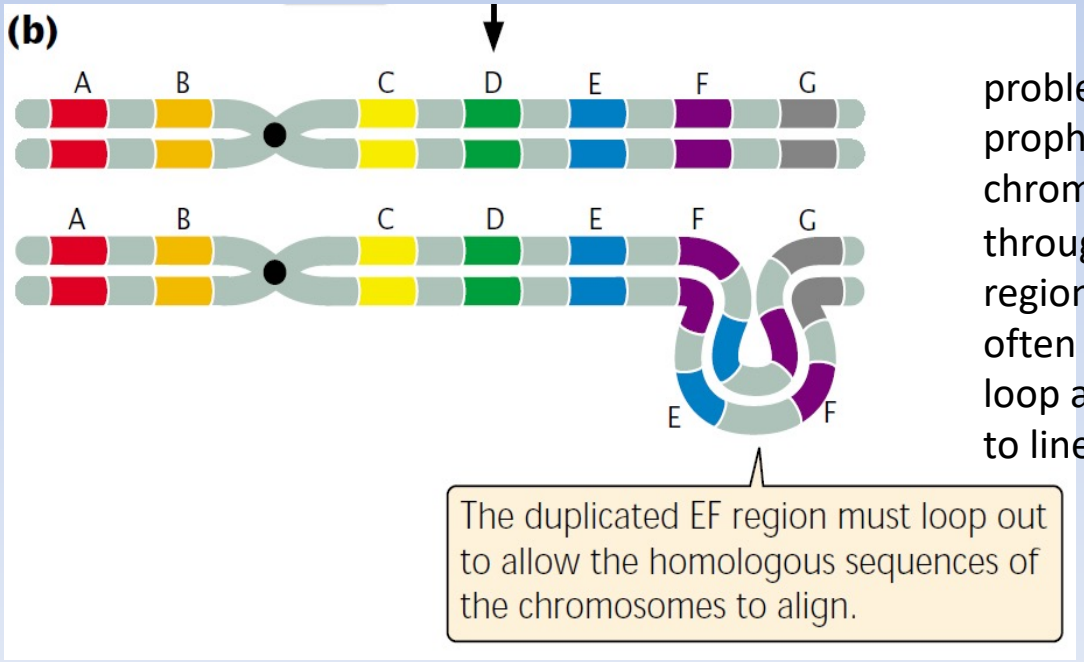
If the duplicated segment is located some distance from the original segment, either on the same chromosome or on a different one, this type is called a

**displaced duplication.**

A duplication can either be in the same orientation as the original sequence,. When the duplication is inverted, it is called a

**reverse duplication**



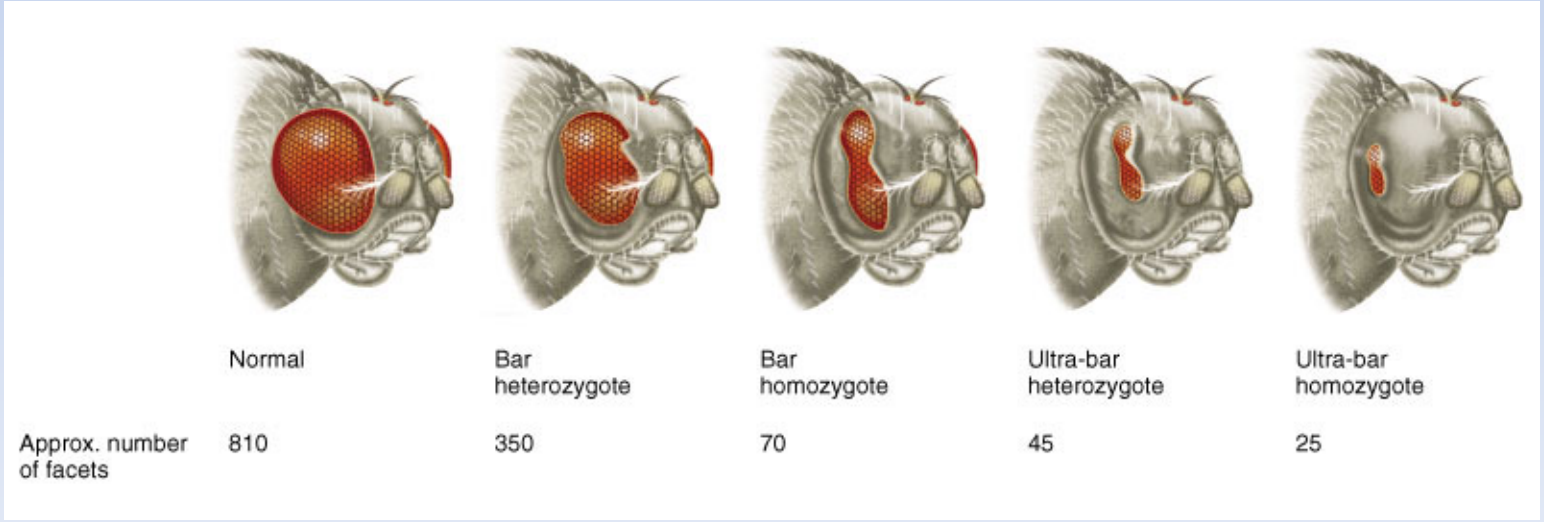

problems arise in chromosome pairing at prophase I of meiosis, because the two chromosomes are not homologous throughout their length. The homologous regions will pair and undergo synapsis, which often requires that one or both chromosomes loop and twist so that these regions are able to line up

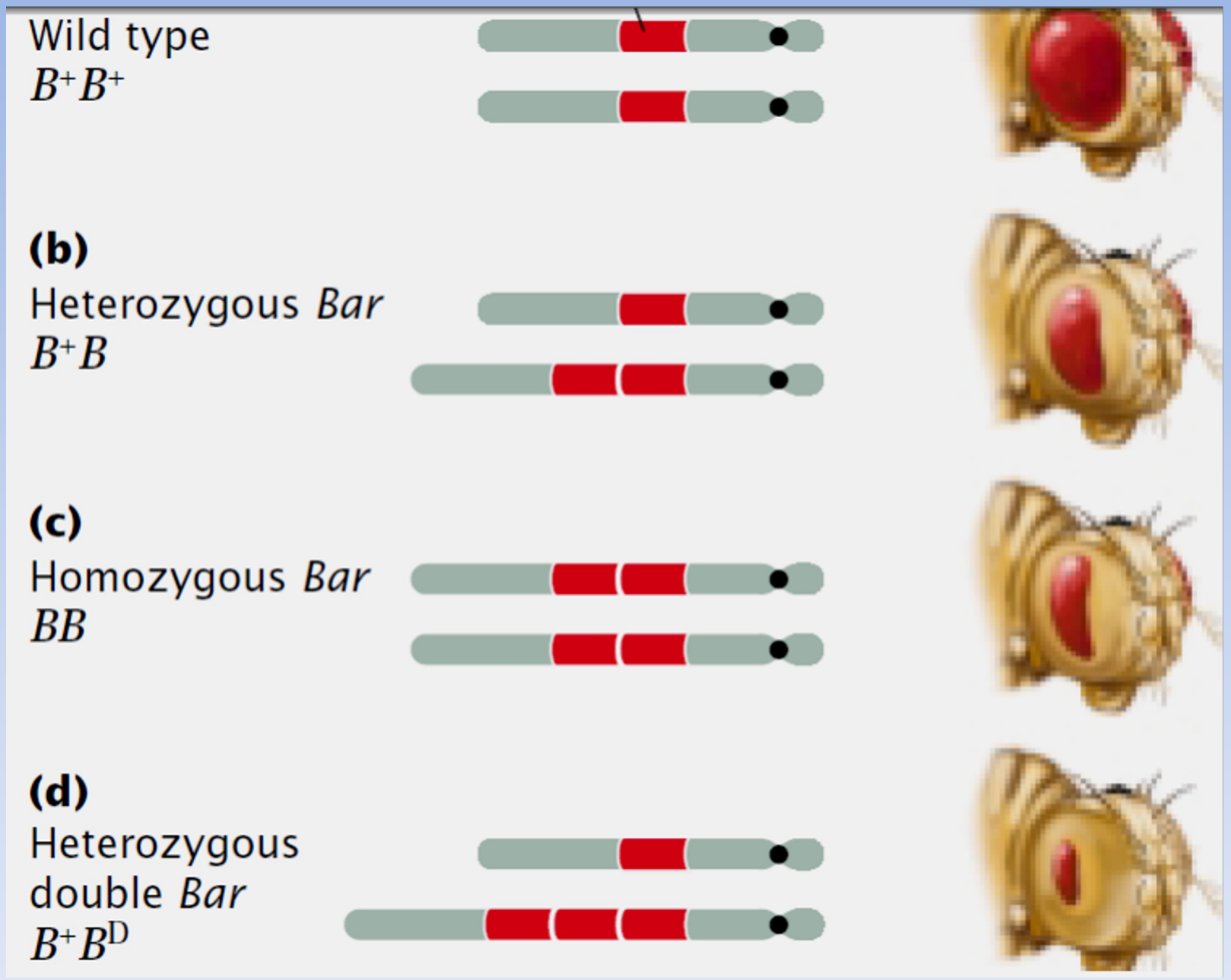
## Sabra Colby Tice (1914)

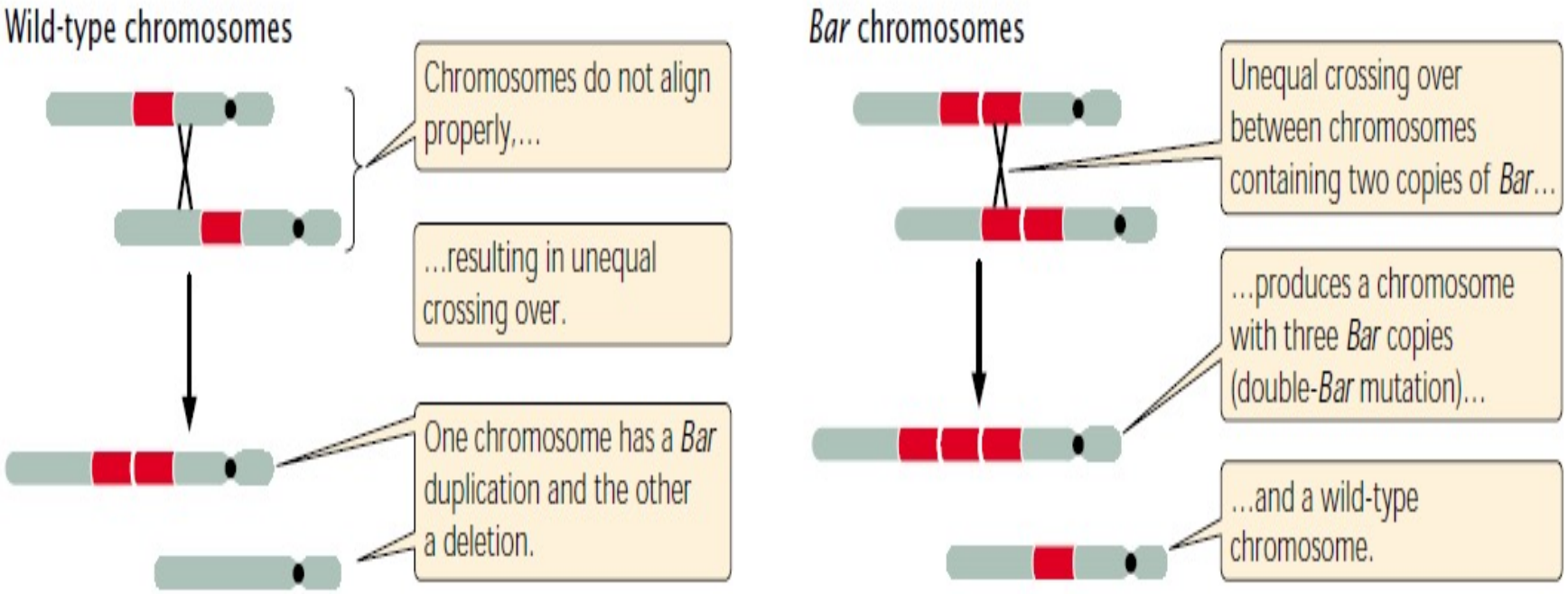
- Discovered a fly with a reduced number of facets in the eye
  - "Bar eyes"
  - X-linked trait
  - Shows incomplete dominance

## Charles Zeleny (1921)

- Identified rare mutants in a true-breeding stock of bar-eyed flies
  - Flies had even fewer facets
  - "Ultra-bar" ("double-bar")
  - Also displayed incomplete dominance



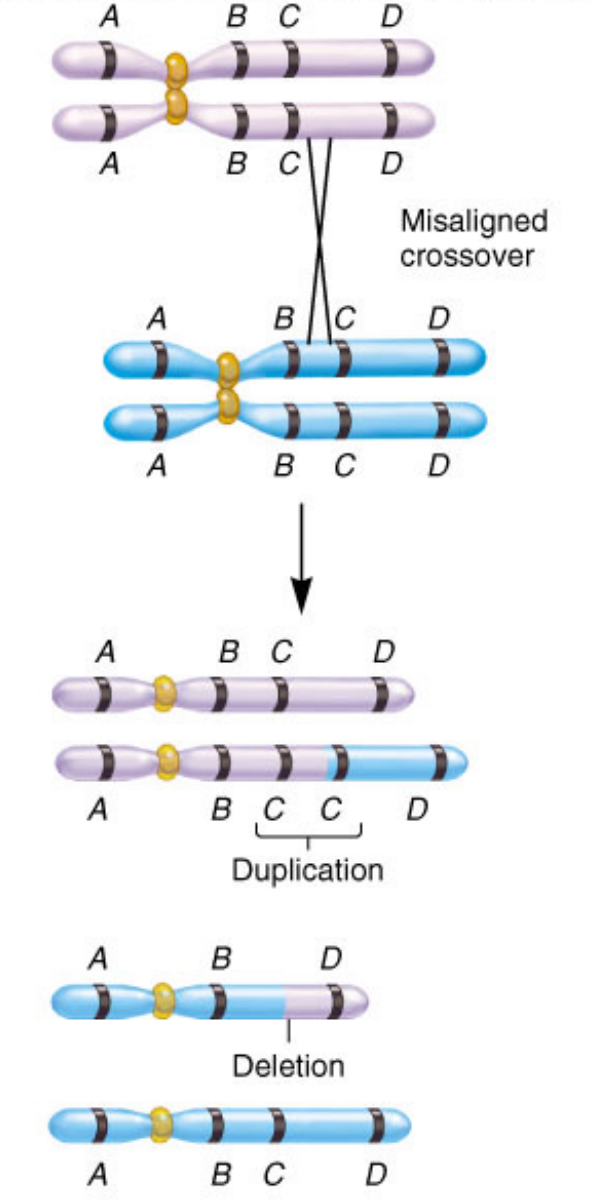

Wild type
$B^+B^+$
(b)
Heterozygous *Bar*
$B^+B$
(c)
Homozygous *Bar*
*BB*
(d)
Heterozygous
double *Bar*
$B^+B^D$




**9.8 Unequal crossing over produces *Bar* and double-*Bar* mutations.**

# Variation in CHROMOSOME STRUCTURE

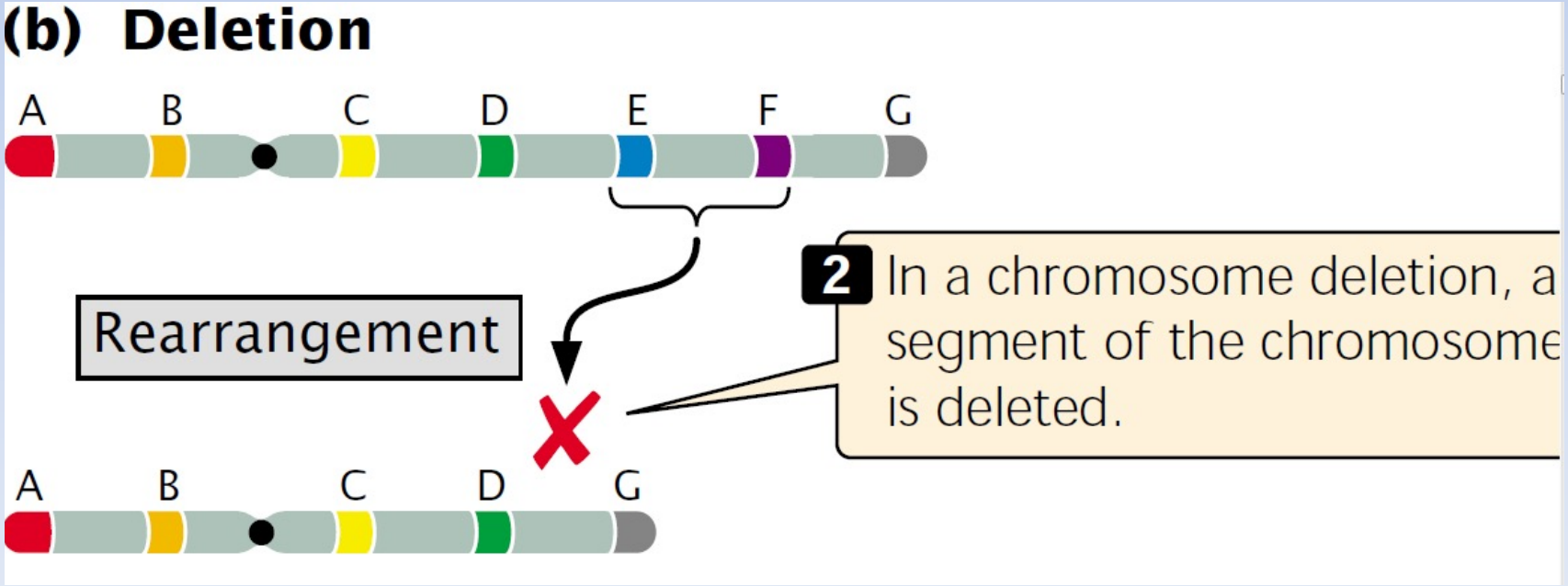
- Duplications result in extra genetic material
  - Usually caused by abnormal events in recombination
    - Crossing over generally occurs at analogous sites in homologous chromosomes
    - Crossovers sometimes occur at misaligned sites
      - Results in one chromosome with a deletion and one chromosome with a duplication
  - Generally happen as rare, sporadic events during the evolution of species
  - Multiple copies of genes can evolve into a family of genes with specialized functions
  - Consequences tend to be correlated with size
  - Small duplications are less likely to have harmful effects than comparable deletions
    - Having one copy of a gene appears less harmful than having three copies



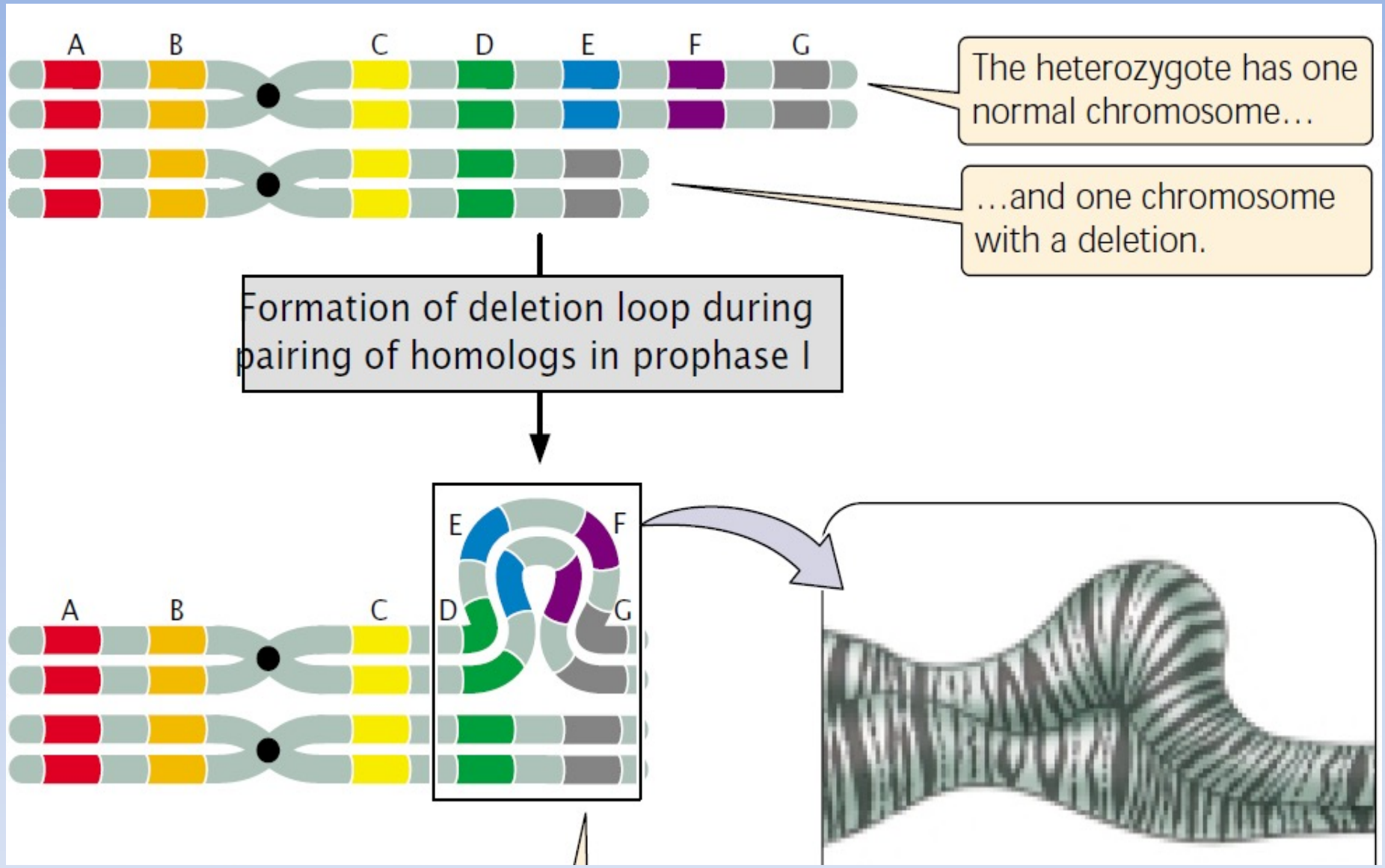
- Relatively few well-defined syndromes result from gene duplications
  - e.g., Charcot-Marie-Tooth disease
    - Caused by a small duplication in the short arm of chromosome 17
    - Relatively common peripheral neuropathy
    - Characterized by numbness in the hands and feet

# Deletions

- A second type of chromosome rearrangement is a **deletion,** the loss of a chromosome segment



- A large deletion can be easily detected because the chromosome is noticeably shortened.
- In individuals heterozygous  for deletions, the normal chromosome must loop out during the pairing of homologs in prophase I of meiosis to allow the homologous regions of the two chromosomes to align and undergo synapsis.
- This looping out generates a structure that looks very much like that seen in individuals heterozygous for duplications.




In prophase I, the normal chromosome must loop out in order for the homologous sequences of the chromosome to align.

# chromosome deletion

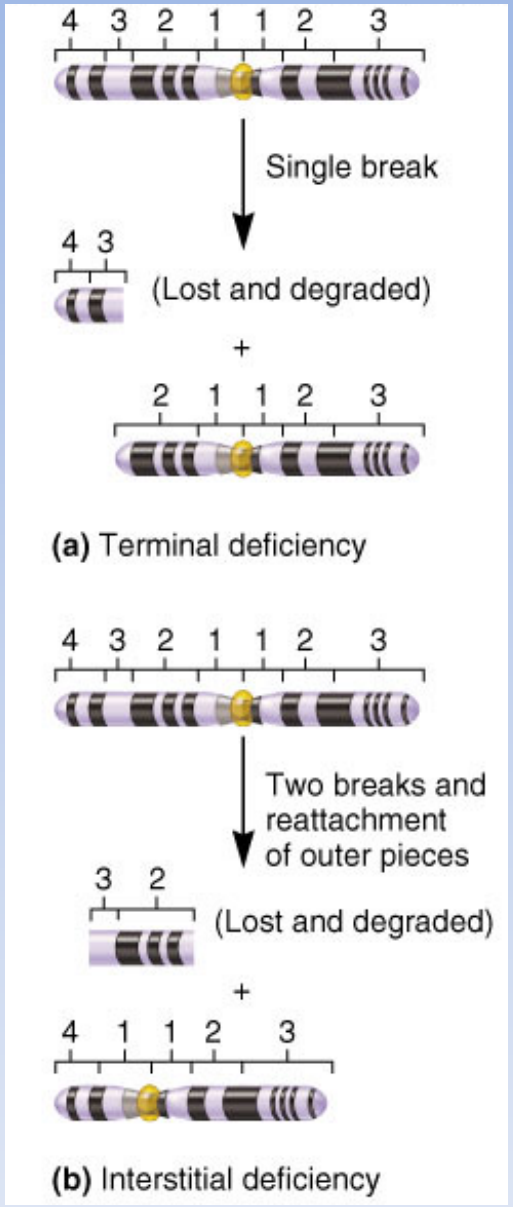
- A chromosome deletion is a mutation in which a part of the chromosome is lost. In individuals heterozygous for a deletion, the normal chromosome loops out during prophase I of meiosis. Deletions do not undergo reverse mutation. They cause recessive genes on the undeleted chromosome to be expressed and cause imbalances in gene products.
- The phenotypic consequences of a deletion depend on which genes are located in the deleted region.
- If the deletion includes the centromere, the chromosome will not segregate in meiosis or mitosis and will usually be lost.
- Many deletions are lethal in the homozygous state because all copies of any essential genes located in the deleted region are missing.

- Even individuals heterozygous for a deletion may have multiple defects for three reasons
- First, the heterozygous condition may produce imbalances in the amounts of gene products,.
- Second
- **Pseudodominance:** deletions may allow recessive mutations on the undeleted chromosome to be expressed
- **Haploinsufficient:** some genes must be present in two copies for normal function loss of function mutations in haploinsufficient genes are dominant

**The Notch phenotype is produced by a chromosome deletion that includes the *Notch gene***

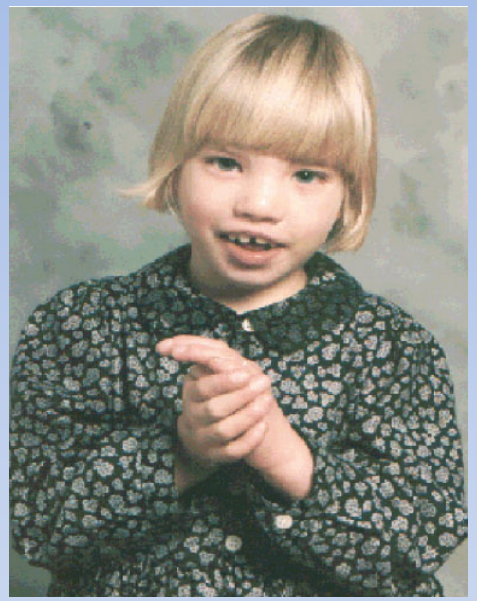
- *Notch is a series* of X-linked wing mutations in *Drosophila that often result* from chromosome deletions.
- *Notch deletions behave as* dominant mutations: when heterozygous for the *Notch* deletion, a fly has wings that are notched at the tips and along the edges
- The *Notch locus is therefore* haploinsufficient—a single copy of the gene is not sufficient to produce a wild-type phenotype

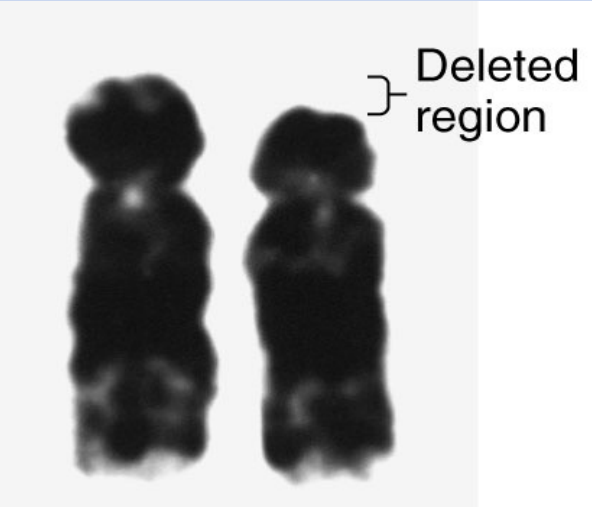
- Chromosomal deficiency
  - Often the result of chromosome breakage
    - Chromosome breaks in one or more places
    - Fragment without a centromere lost and degraded
      - Terminal or interstitial deficiency
  - Consequences depend on size and genes involved
    - Larger deletions tend to be more harmful
  - Many examples of significant phenotypic influences
    - e.g., Cri-du-chat syndrome, Angelman syndrome, Prader-Willi syndrome, various cancers, etc.



# *cri-du-chat syndrome.*

- In humans, a deletion on the short arm of chromosome 5 is responsible for *cri-du-chat syndrome*
- *The name* (French for “cry of the cat”) derives from the peculiar, catlike cry of infants with this syndrome.
- A child who is heterozygous for this deletion has a small head, widely spaced eyes, a round face, and mental retardation.
- Deletion of part of the short arm of chromosome 4 results in another human disorder—
- **Wolf-Hirschhorn syndrome**, which is characterized by seizures and by severe mental and growth retardation.



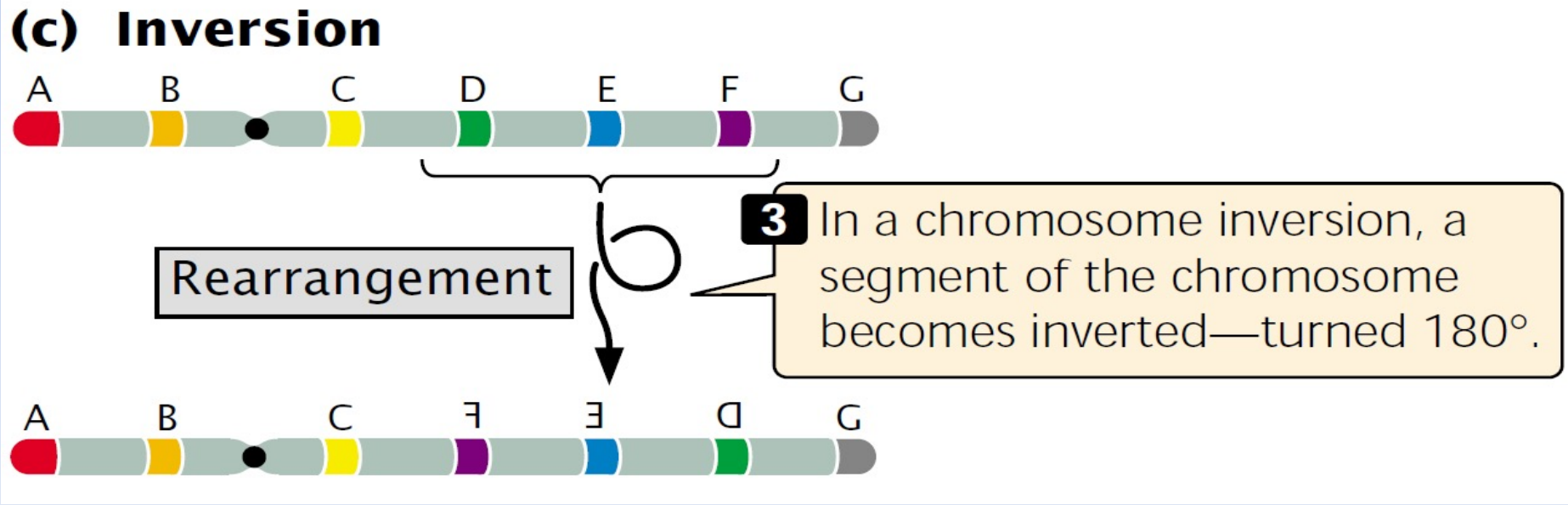


## Table 9.1 Effects of some chromosome rearrangements in humans

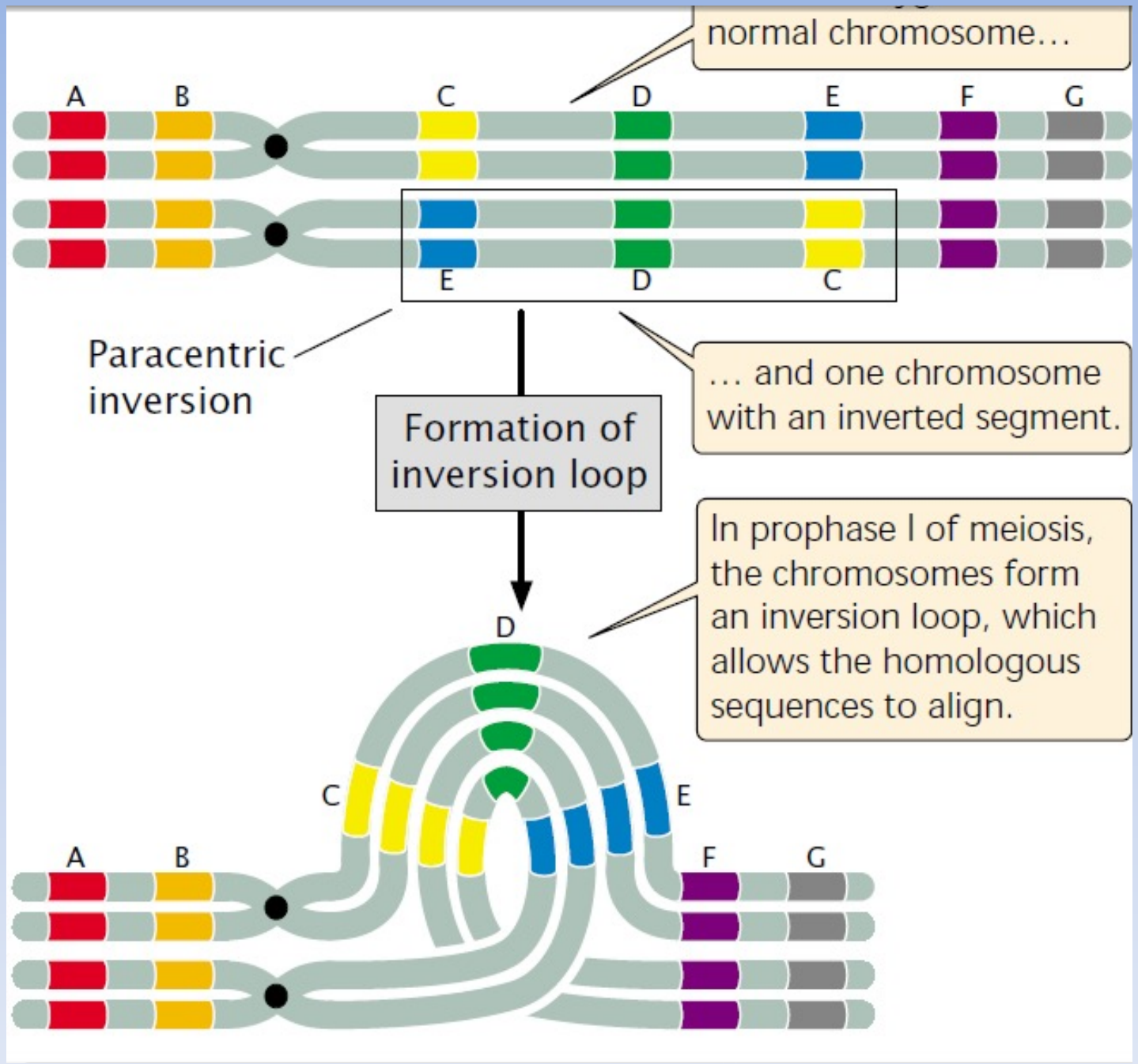
| Type of Rearrangement | Chromosome | Disorder | Symptoms |
|---|---|---|---|
| Duplication | 4, short arm | — | Small head, short neck, low hairline, growth and mental retardation |
| Duplication | 4, long arm | — | Small head, sloping forehead, hand abnormalities |
| Duplication | 7, long arm | — | Delayed development, asymmetry of the head, fuzzy scalp, small nose, low-set ears |
| Duplication | 9, short arm | — | Characteristic face, variable mental retardation, high and broad forehead, hand abnormalities |
| Deletion | 5, short arm | *Cri-du-chat* syndrome | Small head, distinctive cry, widely syndrome spaced eyes, a round face, mental retardation |
| Deletion | 4, short arm | Wolf-Hirschhorn syndrome | Small head with high forehead, wide nose, cleft lip and palate, severe mental retardation |
| Deletion | 4, long arm | — | Small head, mild to moderate mental retardation, cleft lip and palate, hand and foot abnormalities |
| Deletion | 15, long arm | Prader-Willi syndrome | Feeding difficulty at early age, but becoming obese after 1 year of age, mild to moderate mental retardation |
| Deletion | 18, short arm | — | Round face, large low set-ears, mild to moderate mental retardation |
| Deletion | 18, long arm | — | Distinctive mouth shape, small hands, small head, mental retardation |

# Inversions

- **chromosome segment is** inverted—turned 180 degrees
- For an inversion to take place, the chromosome must break in two places.
- Inversions that do not include the centromere, such as AB•CFEDG, are termed
- **paracentric inversions (*para meaning "next to"),***
- inversions that include the centromere, such as ADC• BEFG, are termed **pericentric inversions (*peri meaning*** "around").

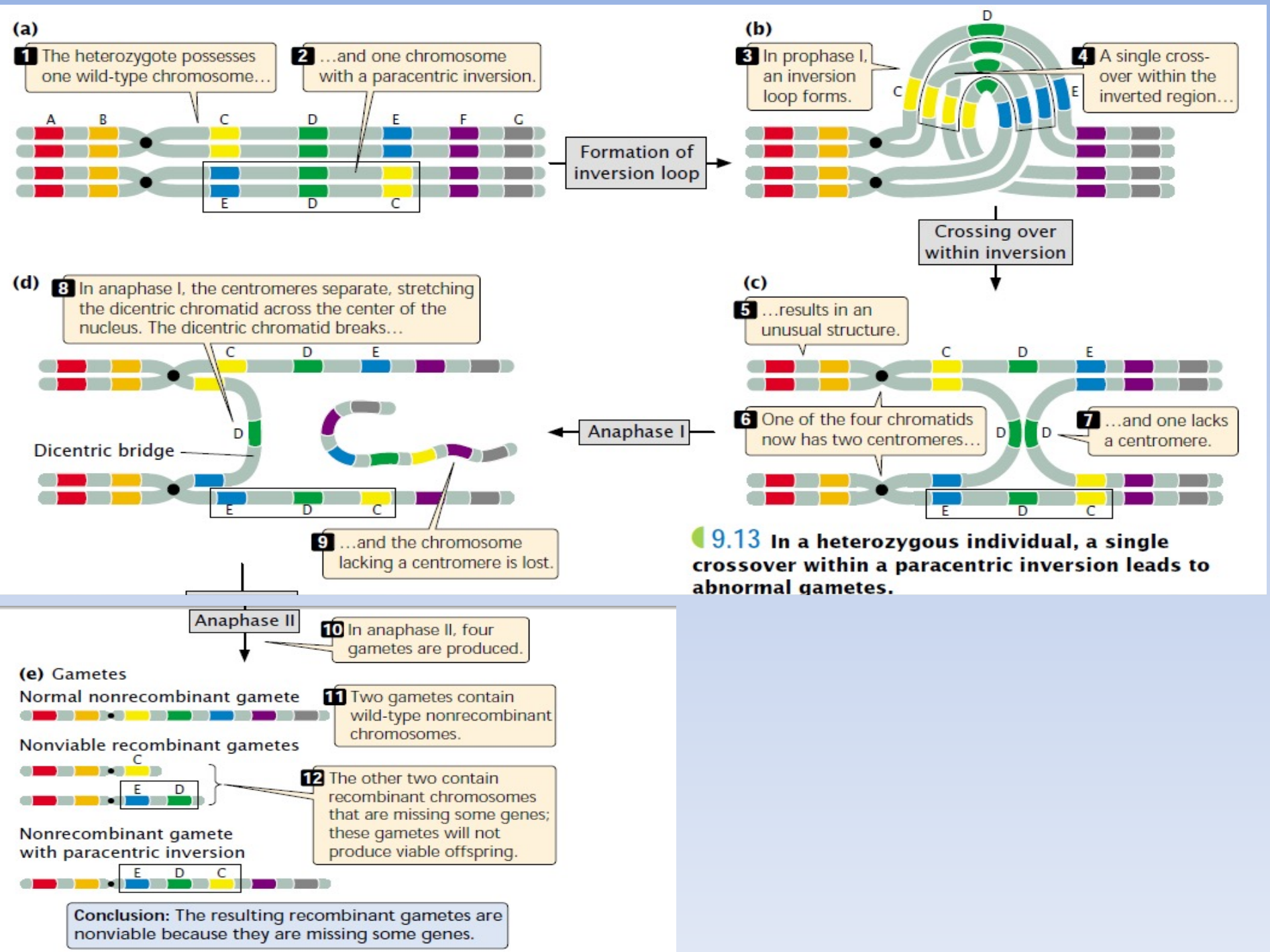


- Individuals with inversions have neither lost nor gained any genetic material; just the gene order has been altered.
- These mutations often have pronounced phenotypic effects.
- An inversion may break a gene into two parts, with one part moving to a new location and destroying the function of that gene.
- Even when the chromosome breaks are between genes, phenotypic effects may arise from the inverted gene order in an inversion.
- Many genes are regulated in a position-dependent manner; if their positions are altered by an inversion, they may be expressed at inappropriate times or in inappropriate tissues.
- This outcome is referred to as a **position effect.**
- When an individual is homozygous for a particular inversion, no special problems arise in meiosis, and the two homologous chromosome can pair and separate normally
- When an individual is heterozygous for an inversion, however, the gene order of the two homologs differs, and the homologous sequences can align and pair only if the two chromosomes form an inversion loop

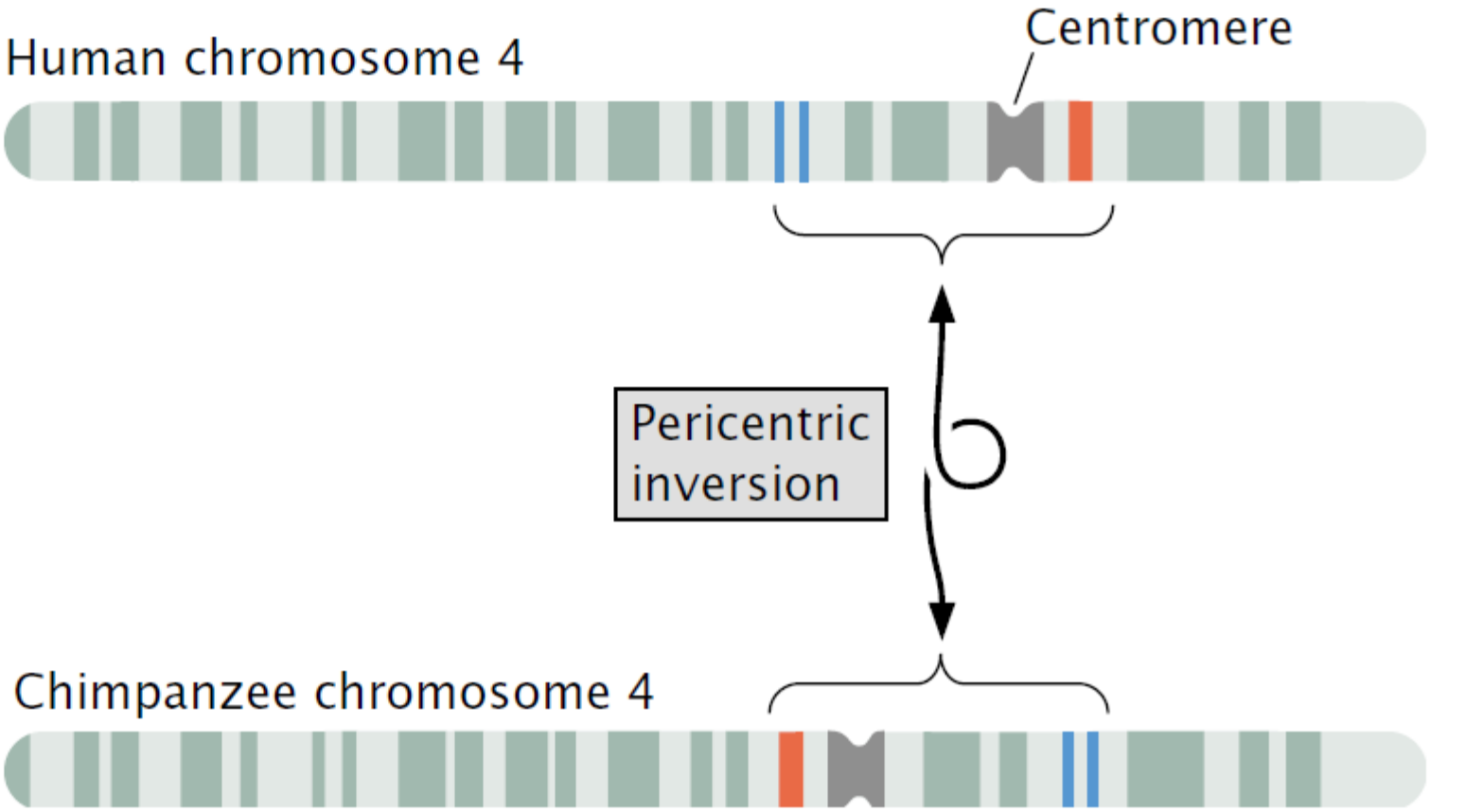

normal chromosome…
A
B
C
D
E
F
G
E
D
C
Paracentric inversion
… and one chromosome with an inverted segment.
Formation of inversion loop
In prophase I of meiosis, the chromosomes form an inversion loop, which allows the homologous sequences to align.
D
C
E
A
B
F
G

# inversion

- In an inversion, a segment of a chromosome is inverted. Inversions cause breaks in some genes and may move others to new locations. In heterozygotes for a chromosome inversion, the chromosomes form loops in prophase I of  meiosis.
- When crossing over takes place within the inverted region, nonviable gametes are usually produced, resulting in a depression in observed recombination frequencies.
- Individuals heterozygous for inversions also exhibit reduced recombination among genes located in the inverted region. The frequency of crossing over within the inversion is not actually diminished but, when crossing over does take place, the result is a tendency to produce gametes that are not viable and thus no recombinant progeny are observed

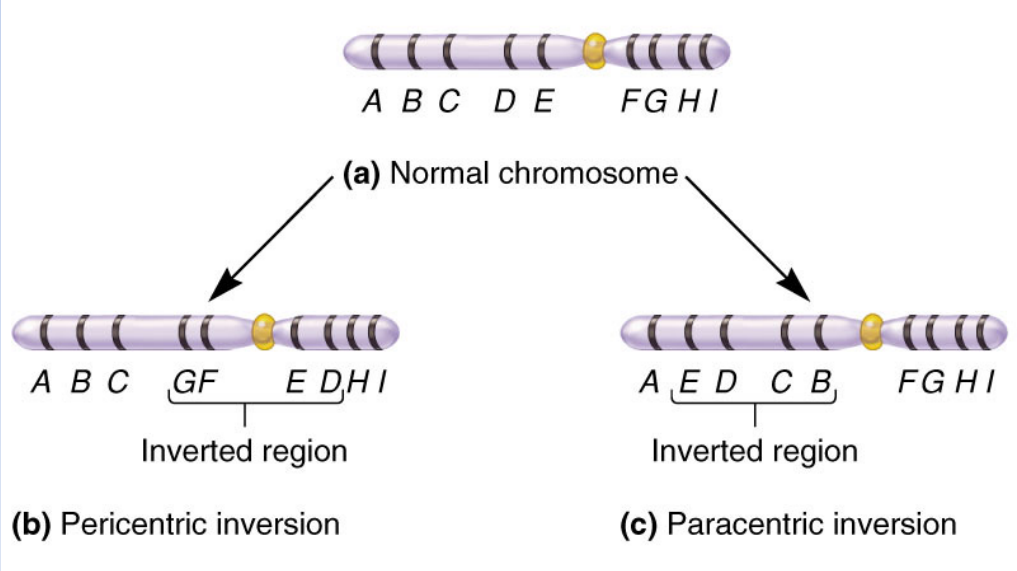



9.13 **In a heterozygous individual, a single crossover within a paracentric inversion leads to abnormal gametes.**

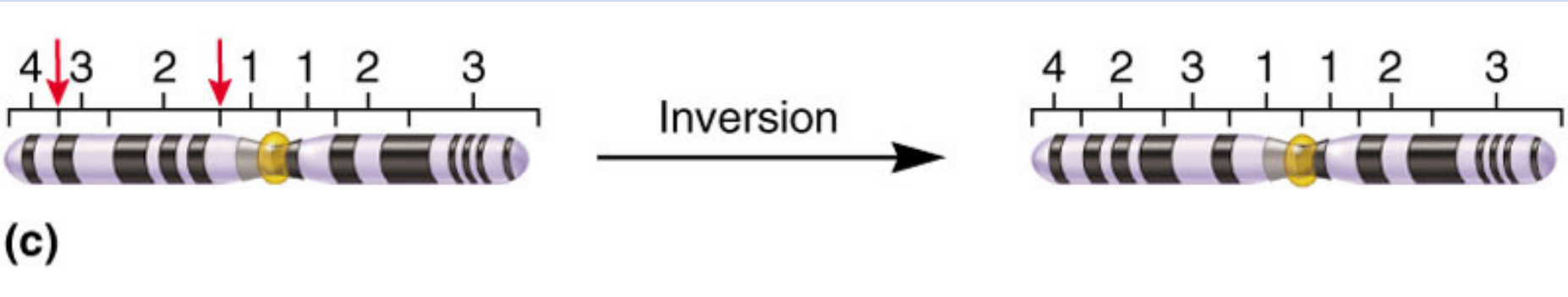



**9.15 Chromosome 4 differs in humans and chimpanzees in a pericentric inversion.**

- Chromosomal inversion
  - Contains a segment that has been flipped to the opposite orientation
    - **Pericentric inversions** include the centromere within the inverted region
    - The centromere lies outside of **paracentric inversions**
- Chromosomal inversion
  - The total amount of genetic material is unchanged
  - Genes within the inverted region are generally transcribed correctly
  - Most inversions have no phenotypic consequences



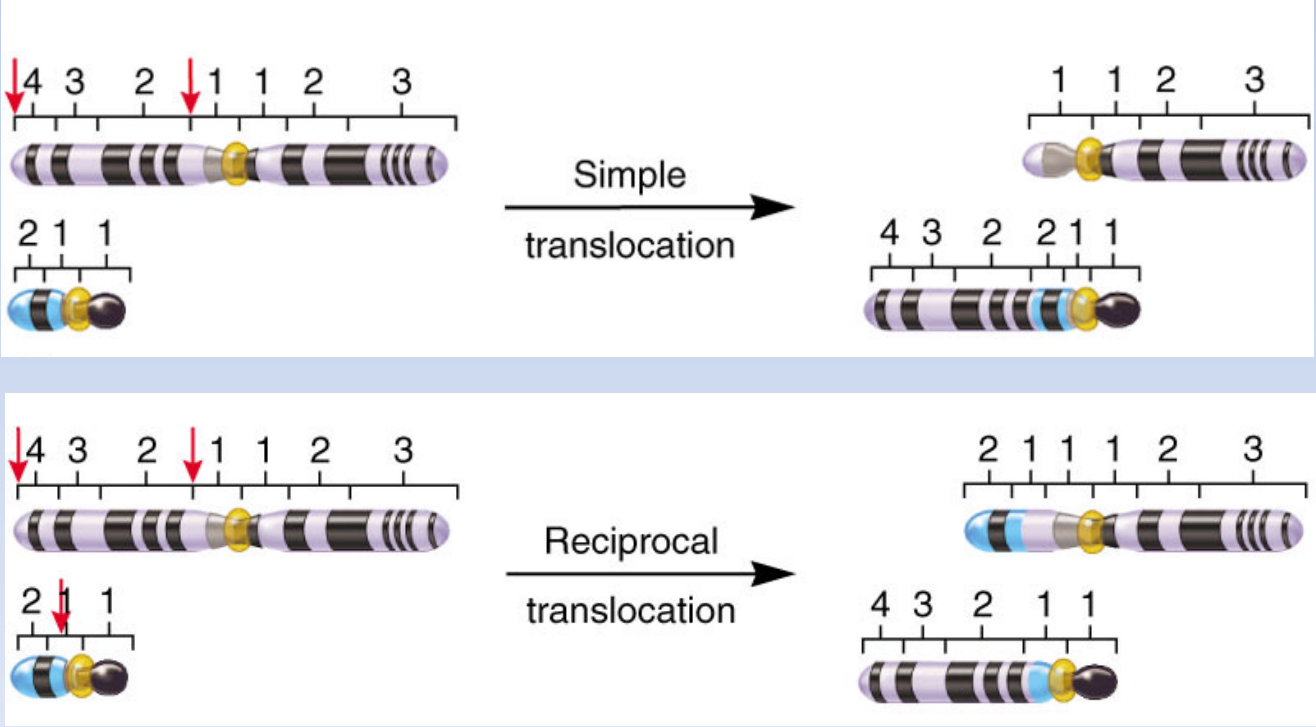
- Chromosomal inversion
  - Rare inversions can result in an altered phenotype
    - Break points within genes can alter the function of the gene
      - e.g., Hemophilia (type A) can be caused by an inversion disrupting the gene for factor VIII
    - Inversion (or translocation) can reposition a gene in a way that alters its normal level of gene expression
      - "Position effect"
  - Surprisingly common
    - ~2% of the human population carry inversions detectable with a light microscope
  - Generally phenotypically normal
  - Some produce offspring with genetic abnormalities



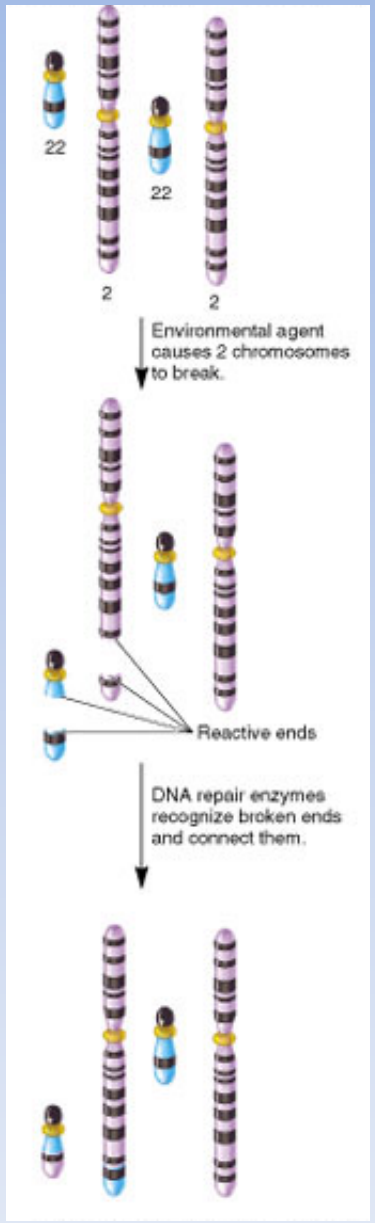
# Translocations

- A **translocation entails the movement of genetic material**.
- In translocations, parts of chromosomes move to other, nonhomologous chromosomes or other regions of the same chromosome.
- Translocations may affect the phenotype by causing genes to move to new locations, where they come under the influence of new regulatory sequences, or by breaking genes and disrupting their function

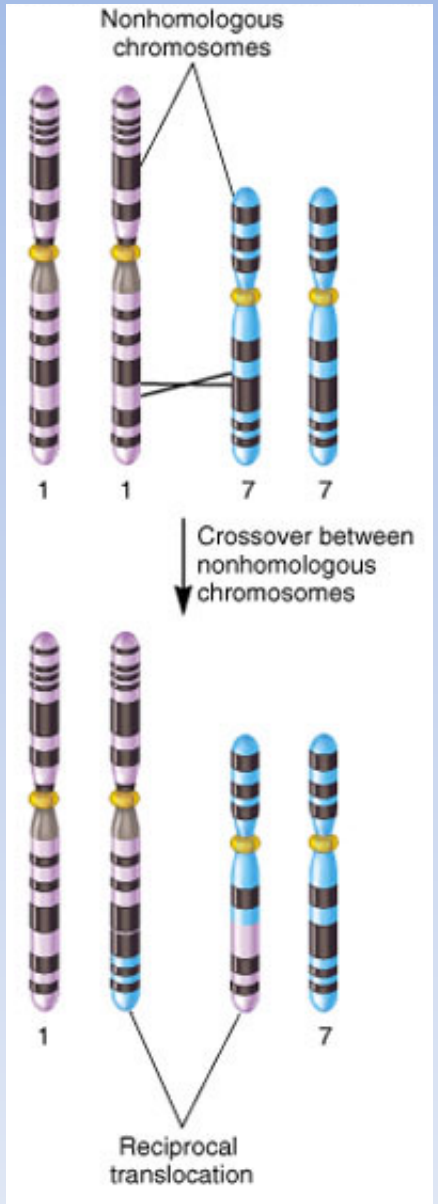
- Translocations
  - Chromosomal rearrangements
  - A portion of a chromosome is attached to a non-homologous chromosome



- Ends of normal chromosomes possess telomeres
  - Contain specialized DNA repeat sequences
  - Prevent attachment of chromosomal DNA to chromosome ends
- Some agents cause chromosomes to break
  - Broken ends lack telomeres
  - DNA repair enzymes may join them together
    - Abnormal chromosomes are formed
    - A **translocation** results

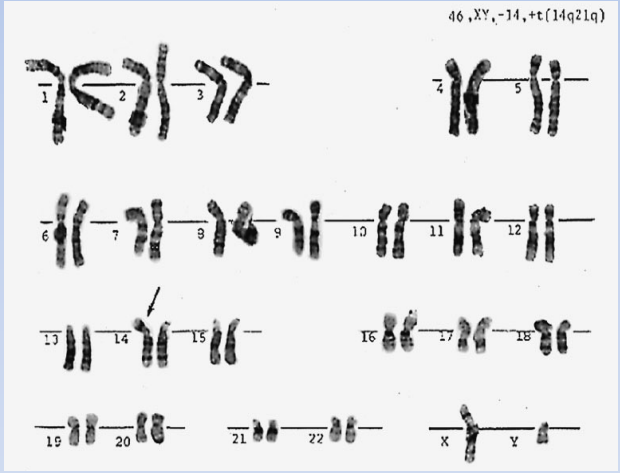


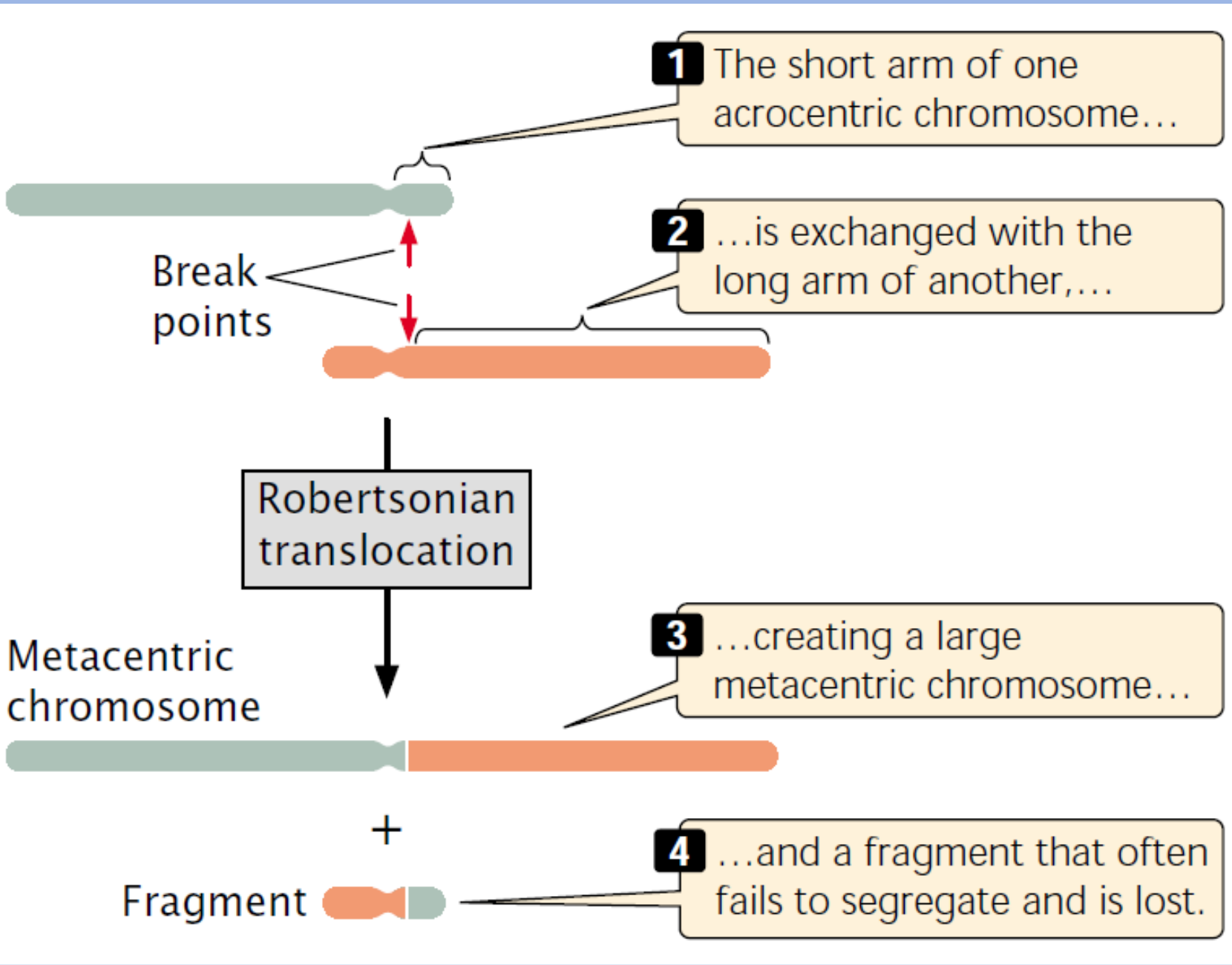
- Translocations
  - Can be formed by crossover between nonhomologous chromosomes
  - No change in the total amount of genetic material
    - "**Reciprocal translocation**"
    - "**Balanced translocation**"



- Balanced translocations
  - Usually no phenotypic consequences
    - Amount of genetic material is normal
    - Rarely, phenotype can be altered due to position effects
  - Inheritance can result in an **unbalanced translocation**
    - Generally associated with phenotypic abnormalities
    - Can be lethal

- Unbalanced translocations
  - Cause of familial Down syndrome
    - Majority of chromosome 21 is attached to chromosome 14
    - Individual has three copies of most of the genes on chromosome 21
    - Characteristics similar to the more common form of Down syndrome
      - Three copies of chromosome 21
- Familial Down syndrome
  - Example of a Robertsonian translocation
  - Most common type of chromosome rearrangement in humans
    - Centromeric regions of two nonhomologous acrocentric chromosomes become fused
    - Breaks at extreme ends of short arms
    - Small acentric fragments are lost
    - Larger chromosomal segments fuse at centromeric regions
    - Chromosome formed is metacentric or submetacentric




1 The short arm of one acrocentric chromosome…
Break points
2 …is exchanged with the long arm of another,…
Robertsonian translocation
Metacentric chromosome
3 …creating a large metacentric chromosome…
+
Fragment
4 …and a fragment that often fails to segregate and is lost.

**Translocations can affect a phenotype in several ways.**

- First, they may create new linkage relations that affect gene expression (a position effect):
- Genes translocated to new locations may come under the control of different regulatory sequences or other genes that affect their expression— an example is found in Burkitt lymphoma

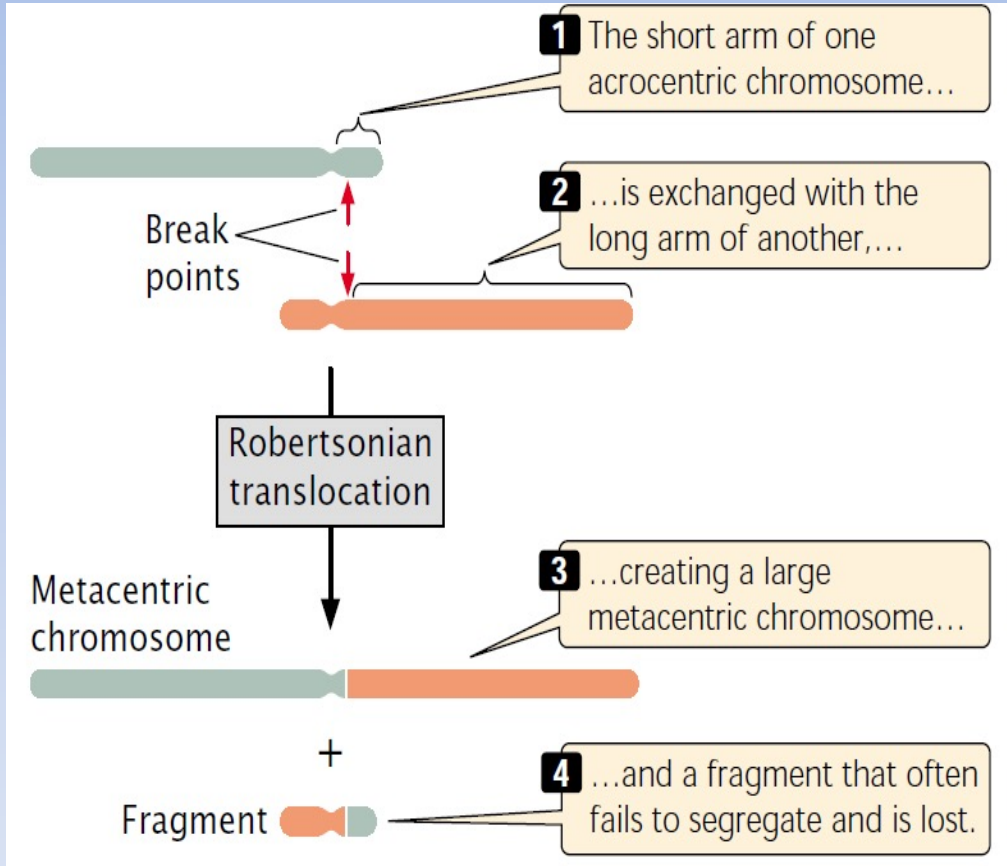
- Second the chromosomal breaks that bring about translocations may take place within a gene and disrupt its function

# Neurofibromatosis

- Genetic disease characterized by numerous fibrous tumors of the skin and nervous tissue; it results from an autosomal dominant mutation
- Linkage studies first placed the locus for neurofibromatosis on chromosome 17. Geneticists later identified two patients with neurofibromatosis who possessed a translocation affecting chromosome 17.
- These patients were assumed to have developed neurofibromatosis because one of the chromosome breaks that occurred in the translocation disrupted a particular gene that causes neurofibromatosis.

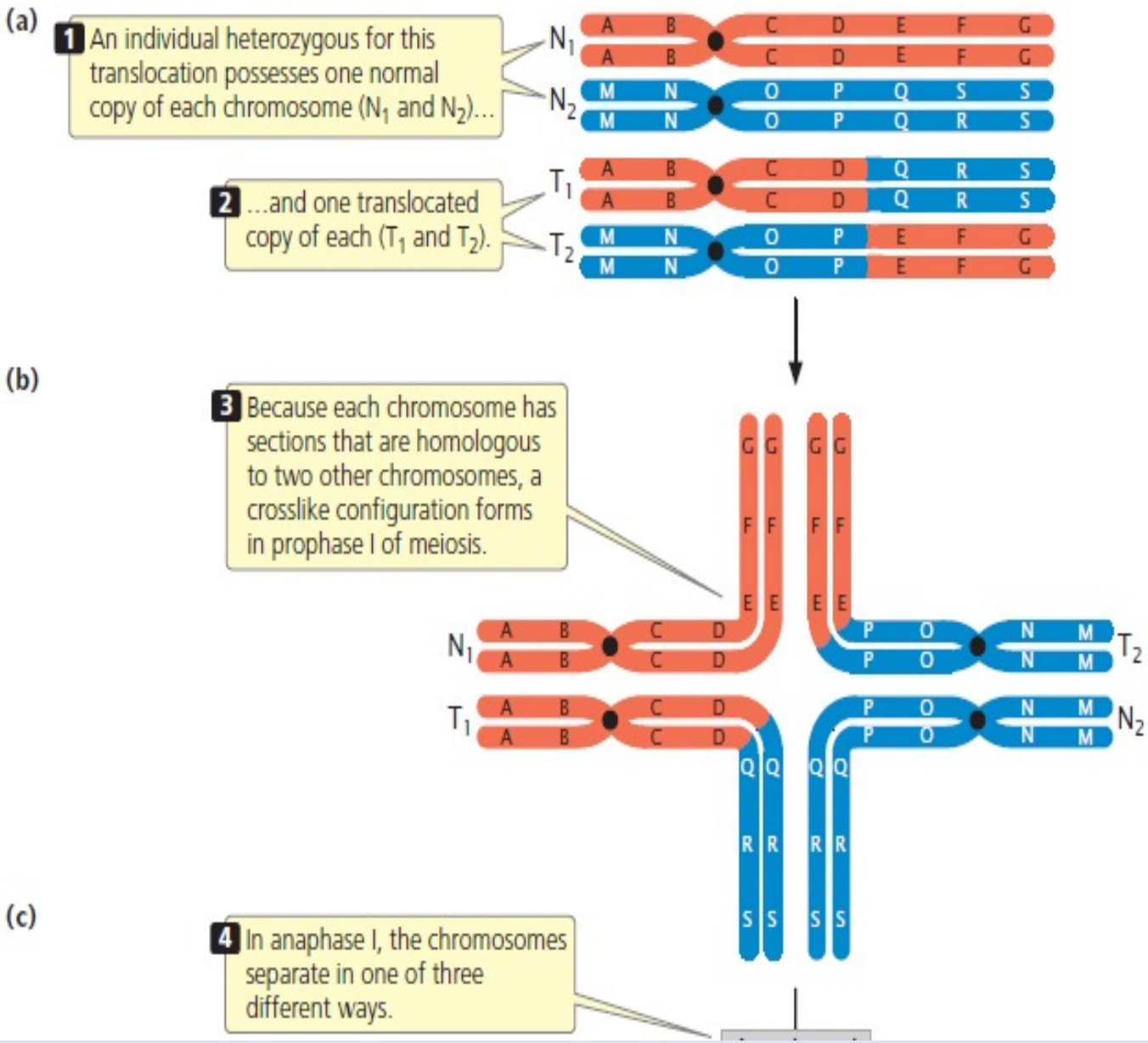
# Robertsonian translocation

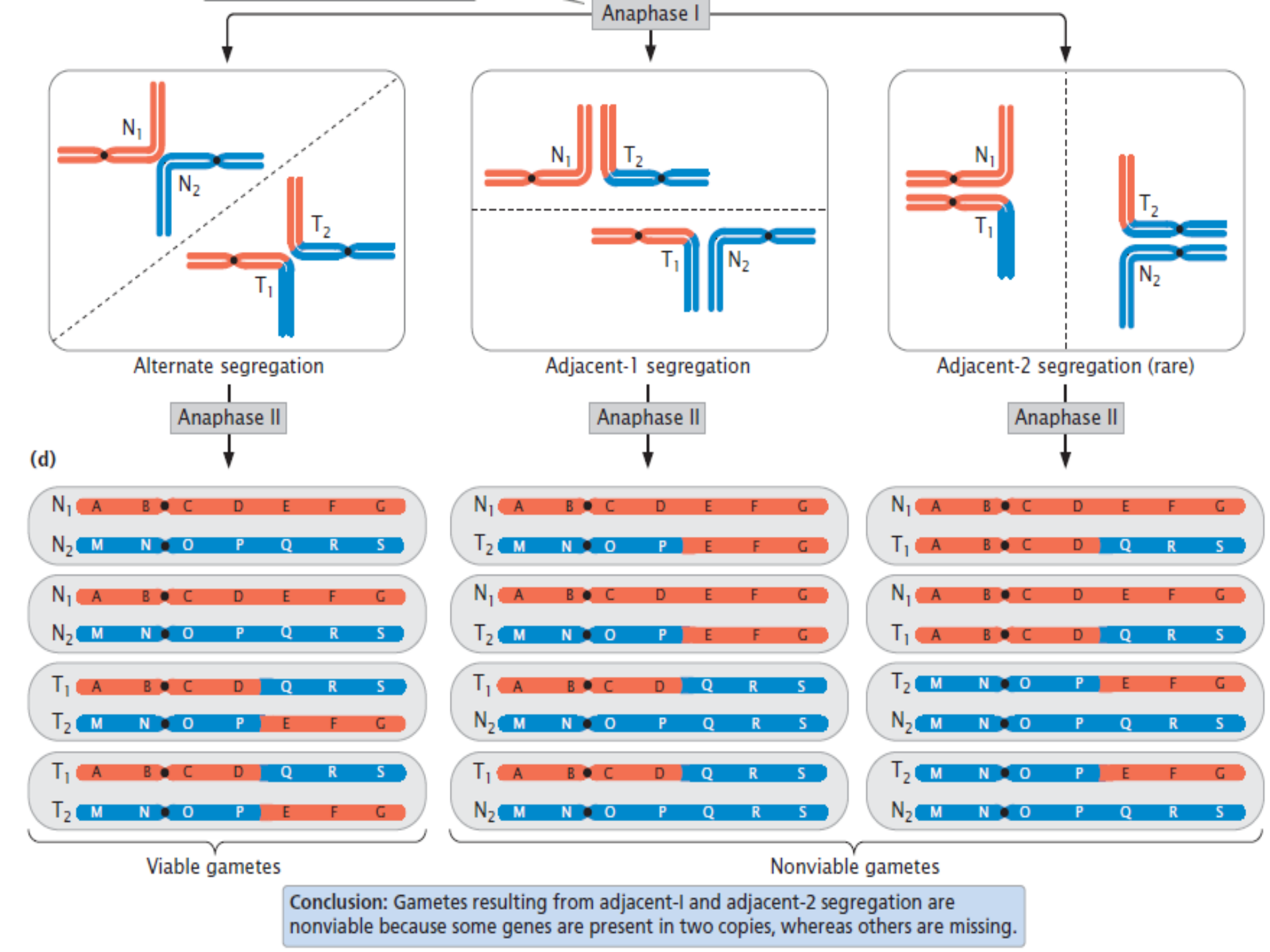
- The long arms of two acrocentric chromosomes become joined to a common centromere through a translocation, generating a metacentric chromosome with two long arms and another chromosome with two very short arms.
- The smaller chromosome often fails to segregate, leading to an overall reduction in chromosome number.
- Robertsonian translocations are the cause of some cases of Down syndrome



# Translocations in meiosis

- The effects of a translocation on chromosome segregation in meiosis depend on the nature of the translocation. Let's consider what happens in an individual heterozygous for a reciprocal translocation.

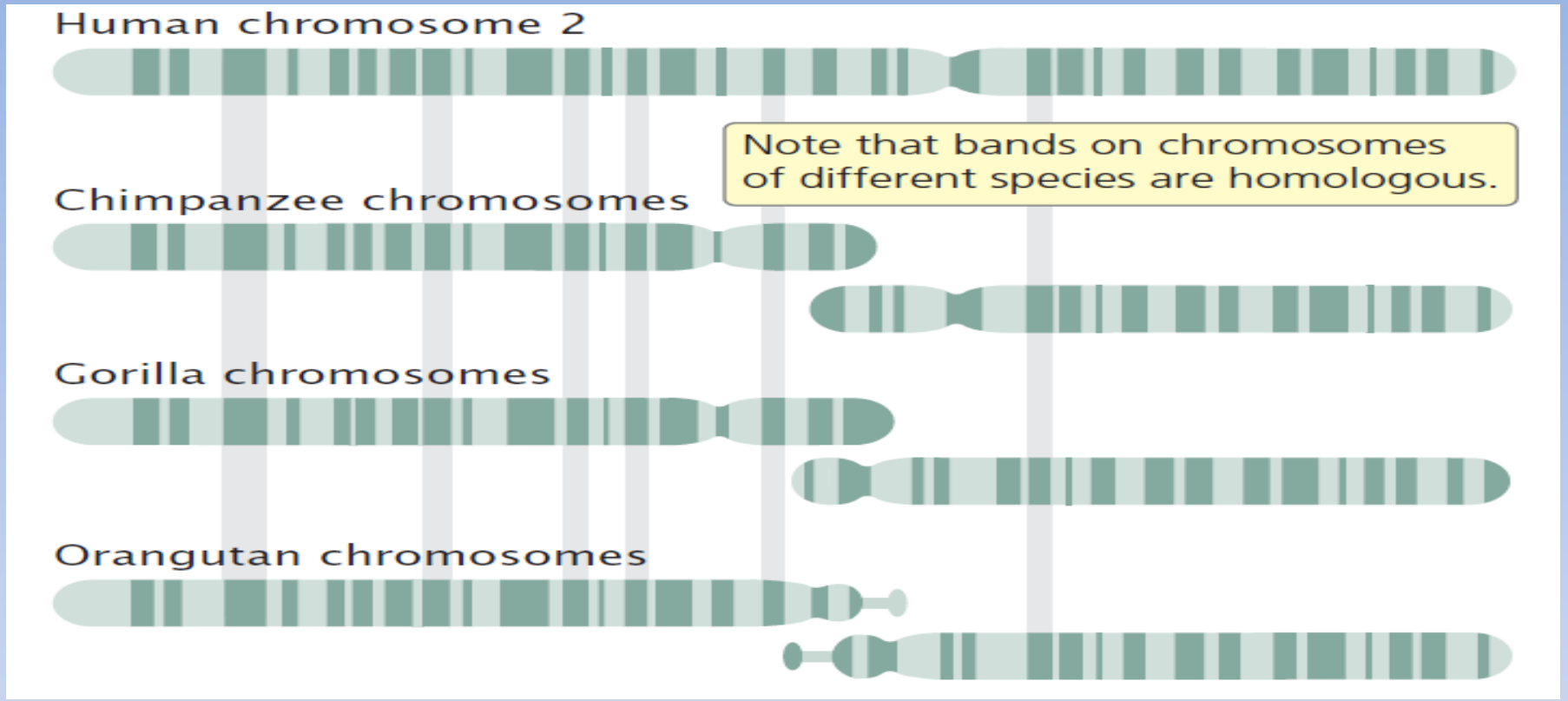

(a)
1 An individual heterozygous for this translocation possesses one normal copy of each chromosome ($N_1$ and $N_2$)...
2 ...and one translocated copy of each ($T_1$ and $T_2$).
(b)
3 Because each chromosome has sections that are homologous to two other chromosomes, a crosslike configuration forms in prophase I of meiosis.
(c)
4 In anaphase I, the chromosomes separate in one of three different ways.




**Conclusion:** Gametes resulting from adjacent-I and adjacent-2 segregation are nonviable because some genes are present in two copies, whereas others are missing.

# The role of translocations in evolution

- Translocations frequently play an important role in the evolution of karyotypes. Chimpanzees, gorillas, and orangutans all have 48 chromosomes, whereas humans have 46.
- Human chromosome 2 is a large, metacentric chromosome with G banding patterns that match those found on two different acrocentric chromosomes of the apes




**Human chromosome 2 contains a Robertsonian translocation that is not present in chimpanzees, gorillas, or orangutans.**

G-banding reveals that a Robertsonian translocation in a human ancestor switched the long and short arms of the two acrocentric chromosomes that are still found in the other three primates. This translocation created the large metacentric human chromosome 2.

# THANK YOU