# Variations in Chromosome Structure & Function

Ch. 8

# INTRODUCTION

- Genetic variation refers to differences between members of the same species or those of different species
  - Allelic variations are due to mutations in particular genes
  - Chromosomal aberrations are substantial changes in chromosome structure
    - These typically affect more than one gene
    - They are also called chromosomal mutations

# Alterations in 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
    - Decrease: Deficiencies/Deletions
    - Increase: Duplications & Insertions
  - 2. The genetic material may remain the same, but is rearranged
    - Inversions
    - Translocations

# Alterations in Chromosome Structure

- Deletion
  - loss of a chromosomal segment
- Duplication
  - repetition of a chromosomal segment
  - Inversion
  - A change in the direction of genetic material along a single chromosome
- Translocation
  - A segment of one chromosome becomes attached to a nonhomologous chromosome
    - Simple translocations
      - One way transfer
    - Reciprocal translocations
      - Two way transfer

# Variations in Chromosome Structure: Deletions

- part of a chromosome is missin
- Deletions start with chromoson breaks induced by:
  - Heat or radiation (especially ionizing).
  - Viruses.
  - Chemicals.
  - Transposable elements.
  - Errors in recombination.
- Deletions do not revert, becaus the DNA is gone (degraded)

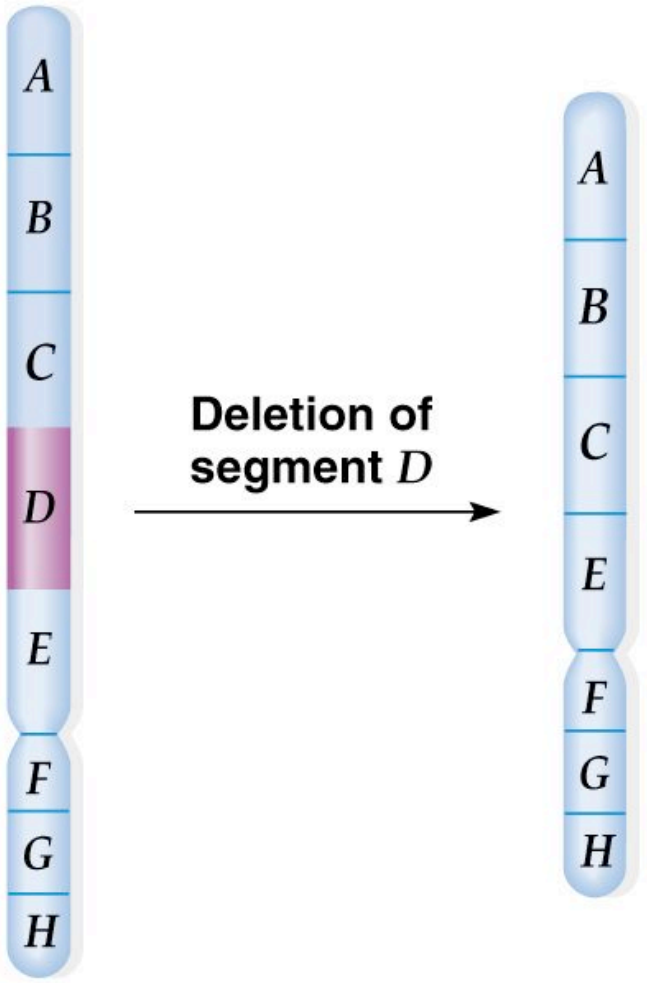



Fig. 8.2 A deletion of a chromosome segment

# Variations in Chromosome Structure: Deletions

- The effect of a deletion depends on what was deleted.
  - A deletion in one allele of a homozygous wild-type organism may give a normal phenotype
    - while the same deletion in the wild-type allele of a heterozygote would produce a mutant phenotype.
  - Deletion of the centromere results in an acentric chromosome that is lost, usually with serious or lethal consequences.
    - No known living human has an entire autosome deleted from the genome.

# Variations in Chromosome Structure: Deletions

- Human disorders caused by large chromosomal deletions are generally seen in heterozygotes, since homozygotes usually die.
  - The number of gene copies is important.
  - Syndromes result from the loss of several to many genes.
- Examples of human disorders caused by large chromosomal deletions:
  - Cri-du-chat ("cry of the cat") syndrome (OMIM 123450), resulting from deletion of part of the short arm of chromosome 5 (Figure 8.4).
  - The deletion results in severe mental retardation and physical abnormalities.

# Variations in Chromosome Structure: Duplications

- Duplications result from doubling of chromosomal segments, and occur in a range of sizes and locations (Figure 8.5).

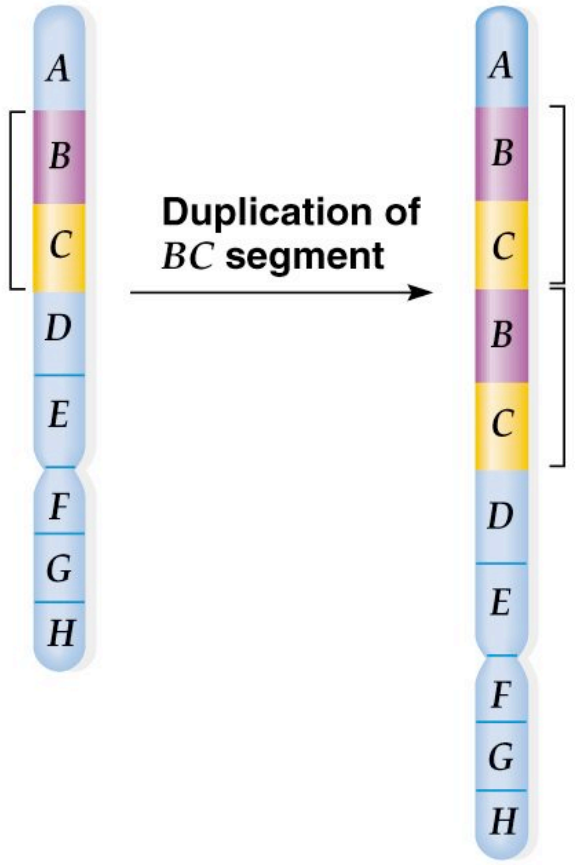



Fig. 8.5 Duplication, with a chromosome segment repeated

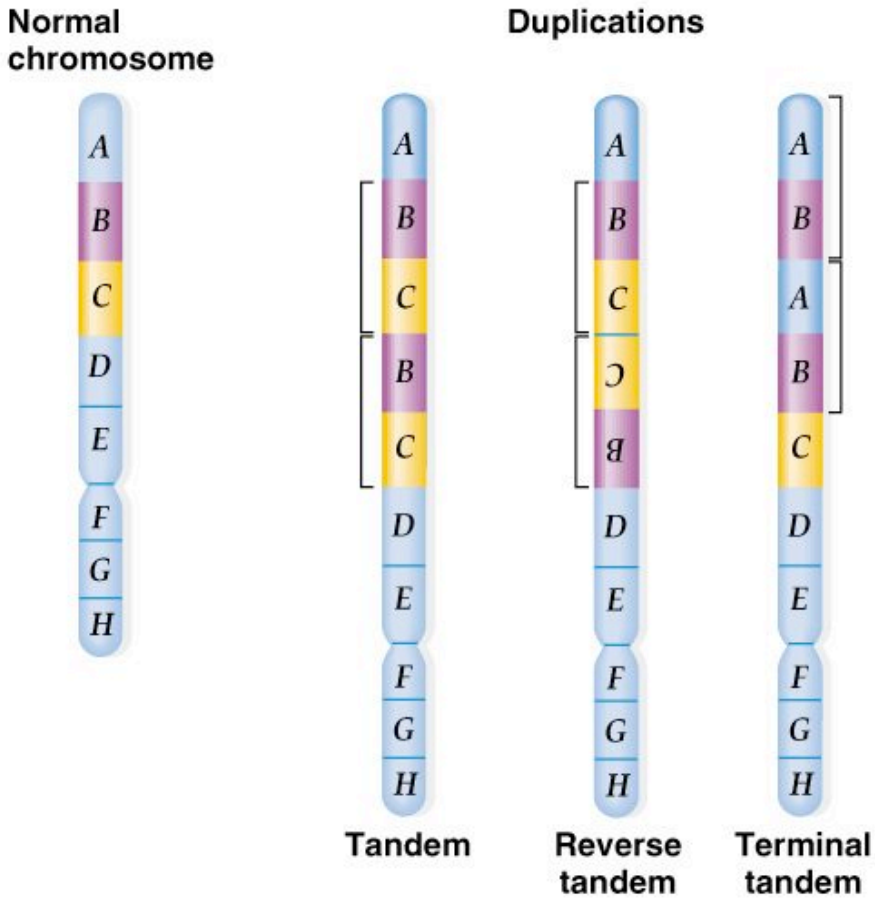
# Variations in Chromosome Structure: Duplications

–Tandem duplications are adjacent to each other.

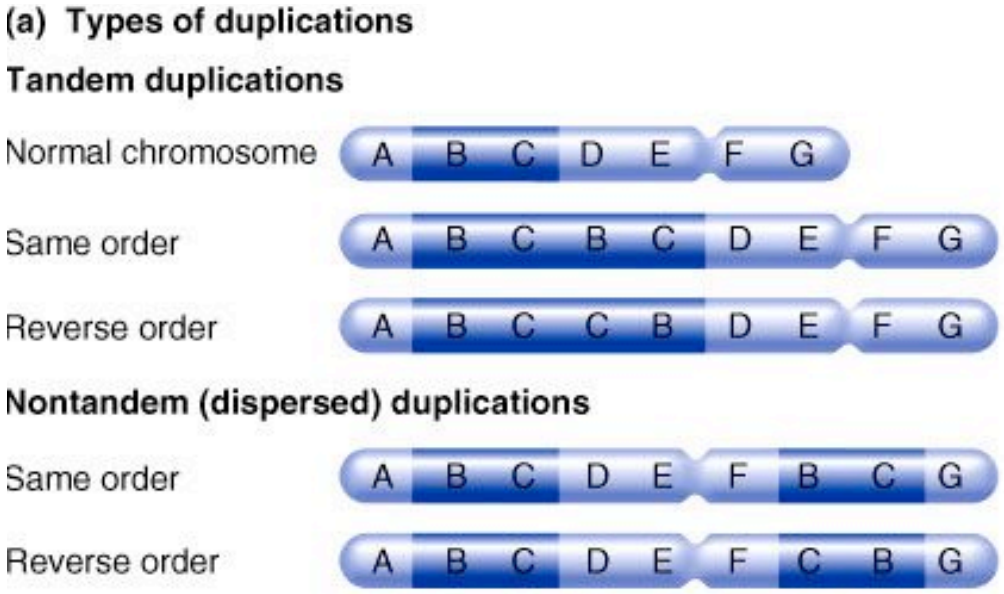
–Reverse tandem duplications result in genes arranged in the opposite order of the original.

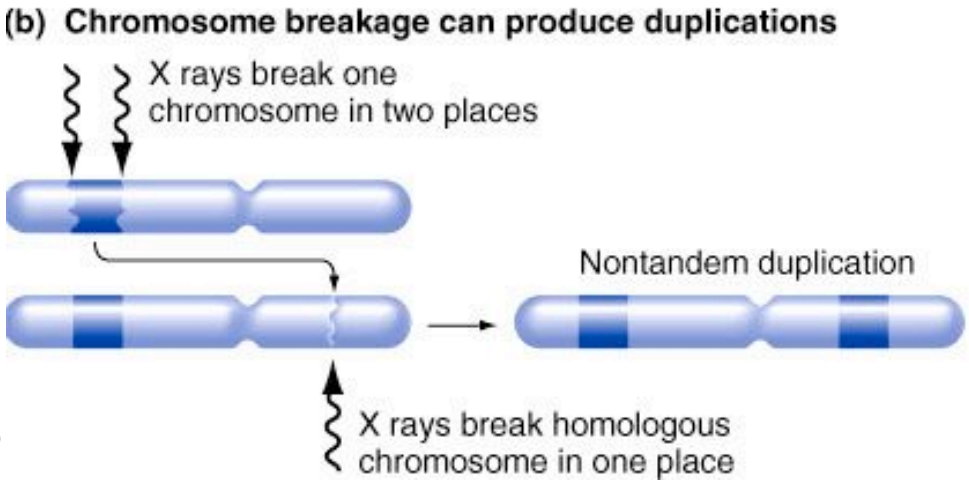
–Tandem duplication at the end of a chromosome is a terminal tandem duplication

– (Figure 8.6).



# Duplications add material to the genome

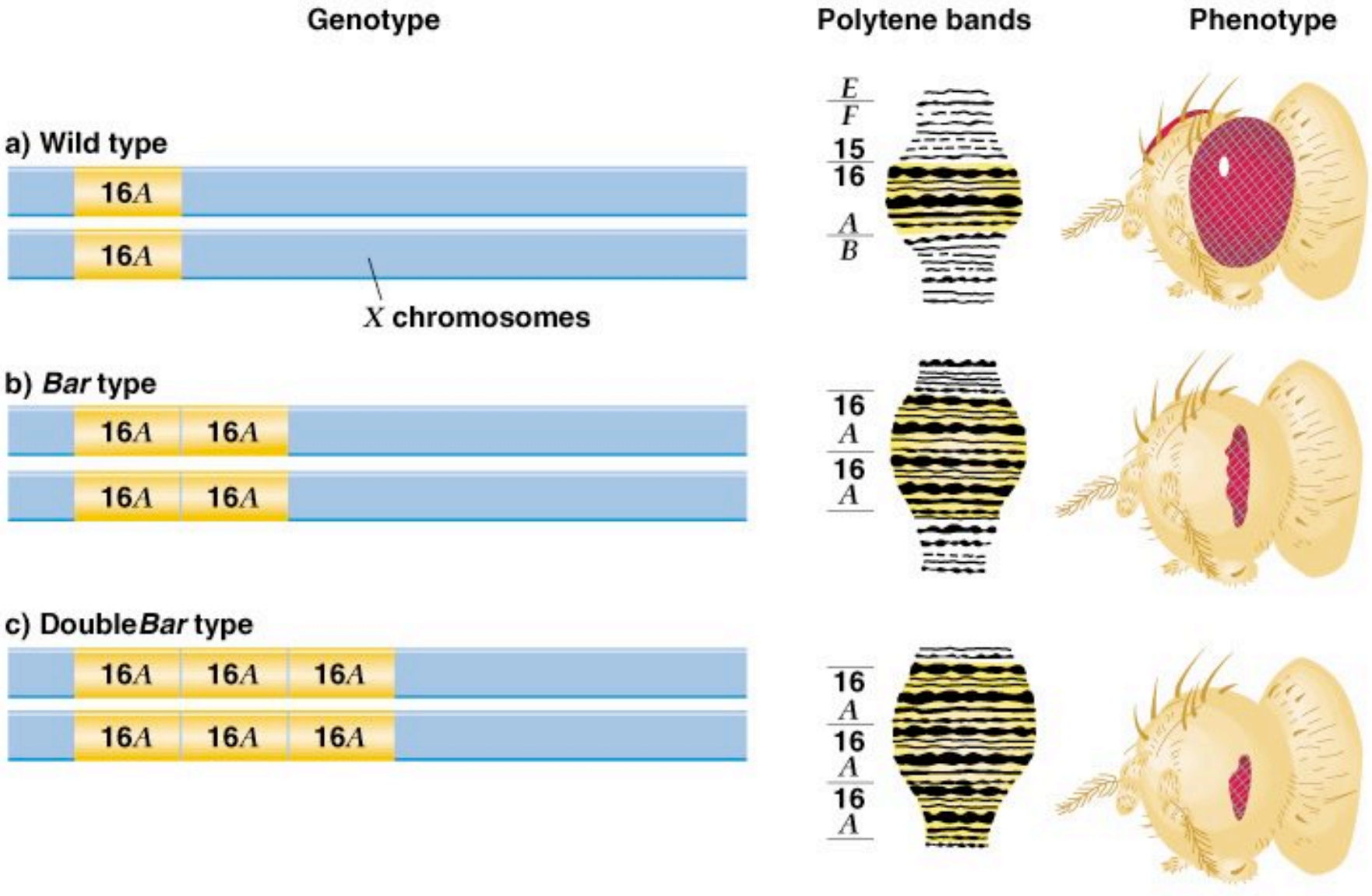


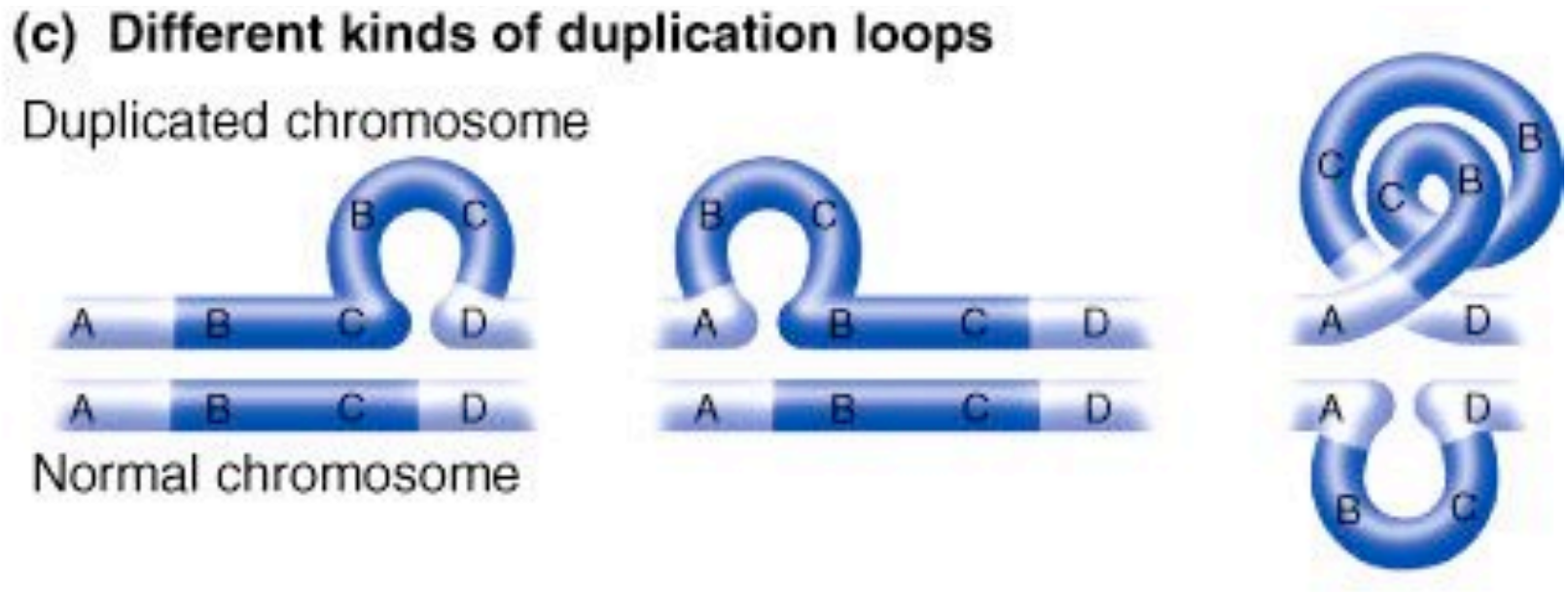
# Variations in Chromosome Structure: Duplications

- An example is the *Drosophila* eye shape allele, *Bar*, that reduces the number of eye facets, giving the eye a slit-like rather than oval appearance
- (Figure 8.7).
  - The *Bar* allele resembles an incompletely dominant mutation:
    - Females heterozygous for *Bar* have a kidney-shaped eye that is larger and more faceted than that in a female homozygous for *Bar*.
    - Males hemizygous for *Bar* have slit-like eyes like those of a *Bar*/*Bar* female.
  - Cytological examination of chromosomes showed that the *Bar* allele results from duplication of a small segment (16A) of the X chromosome.

# Fig. 8.7 Chromosome of *Drosophila* strains



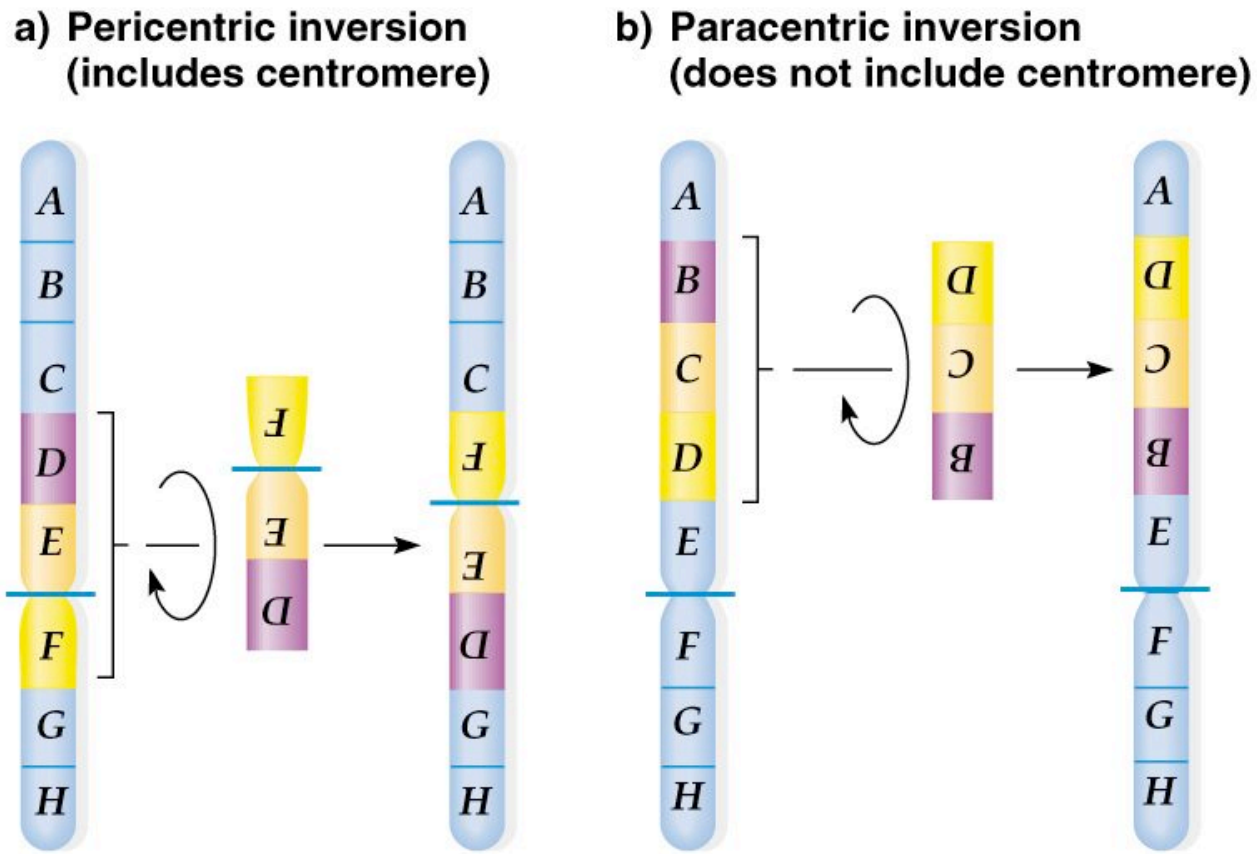
# Duplication loops form when chromosomes pair in duplication heterozygotes




- In prophase I, the duplication loop can assume different configurations that maximize the pairing of related regions

# Variations in Chromosome Structure: Inversions

- Inversion results when a chromosome segment excises and reintegrates oriented 180° from the original orientation.
  - There are two types (Figure 8.8):

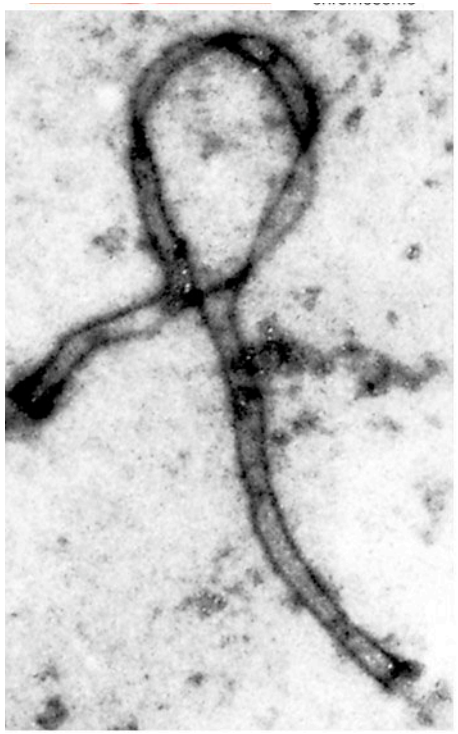


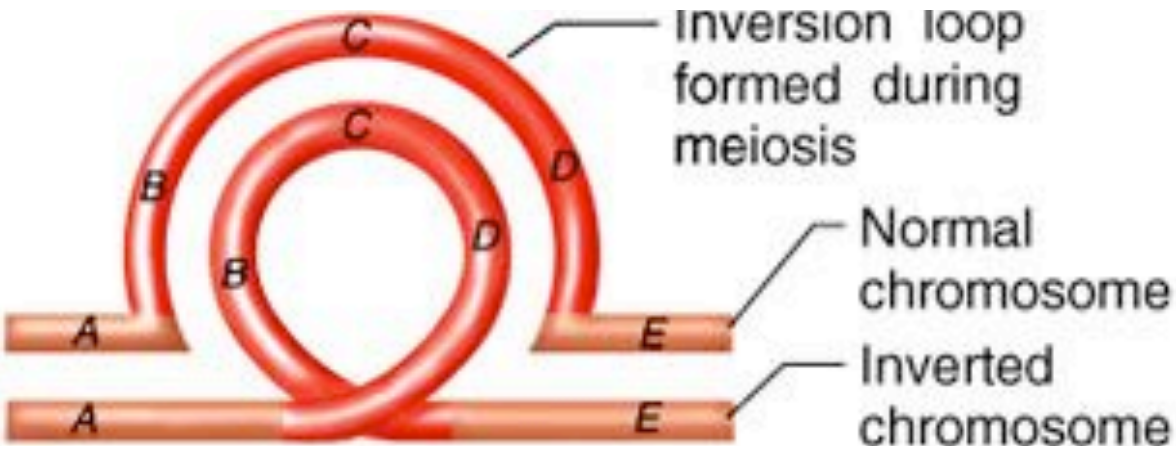
# Variations in Chromosome Structure: Inversions

- Linked genes are often inverted together.
  - The meiotic consequence depends on whether the inversion occurs in a homozygote or a heterozygote.
- A homozygote will have normal meiosis.
- The effect in a heterozygote depends on whether crossing-over occurs.
  - If there is no crossing-over, no meiotic problems occur.
  - If crossing-over occurs in the inversion, unequal crossover may produce serious genetic consequences.

# Inversion heterozygotes reduce the number of recombinant progeny

- Inversion loop in heterozygote forms tightest possible alignment of homologous regions



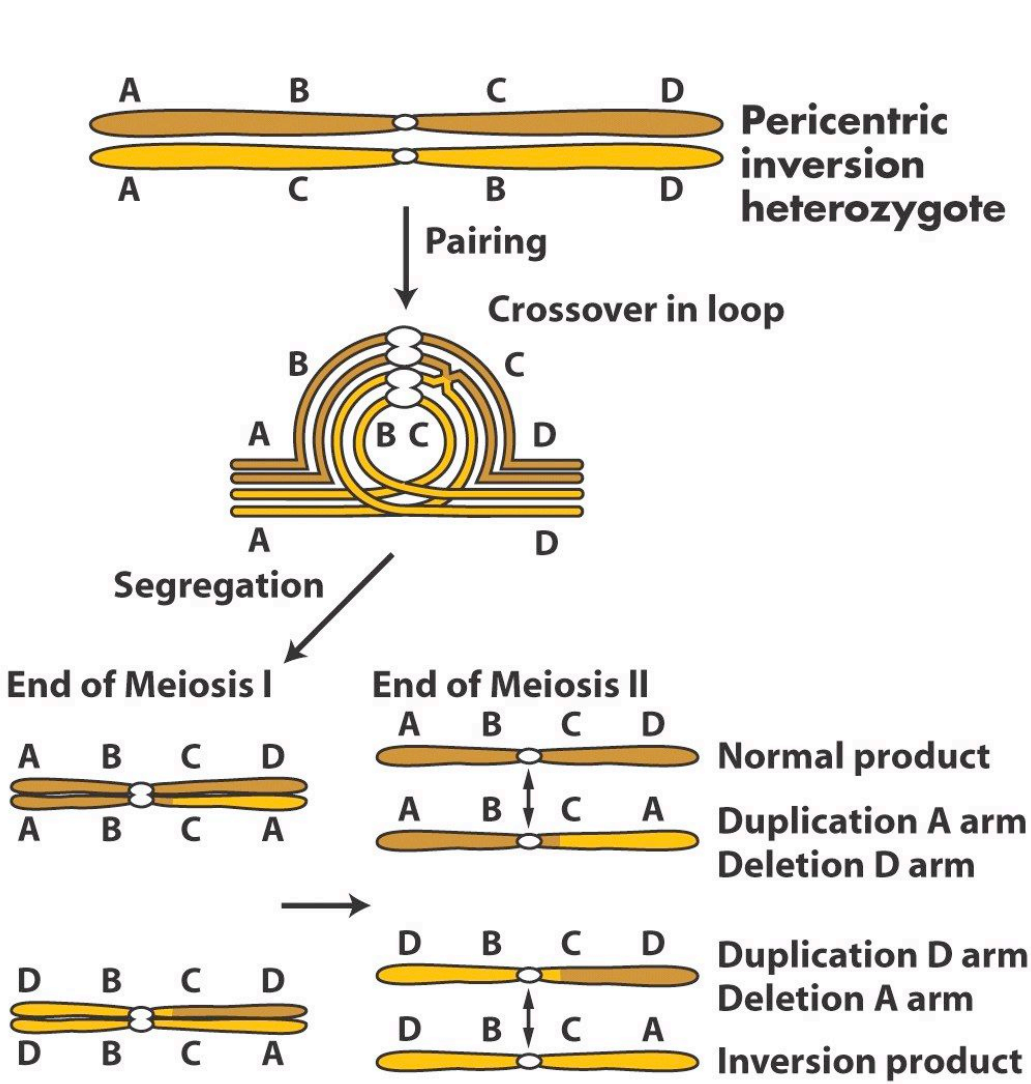


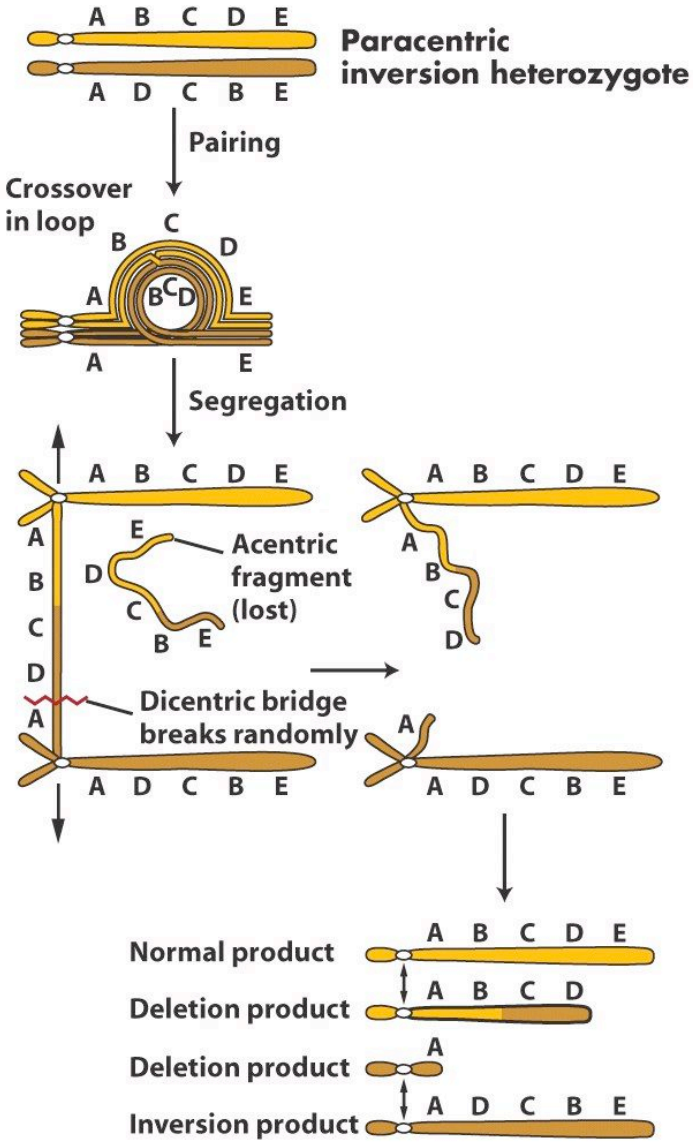
# Recombination involving inversions

- Heterozygous Pericentric Inversion:
  - One normal gamete
  - One gamete with inversion
  - One gamete with a duplication and deletion.
  - One gamete with reciprocal duplication and deletion.

- Heterozygous Paracentric Inversion:
  - One normal gamete
  - One gamete with inversion
  - Two deletion products
  - Some material lost.

# Gametes produced from pericentric and paracentric inversions are imbalanced



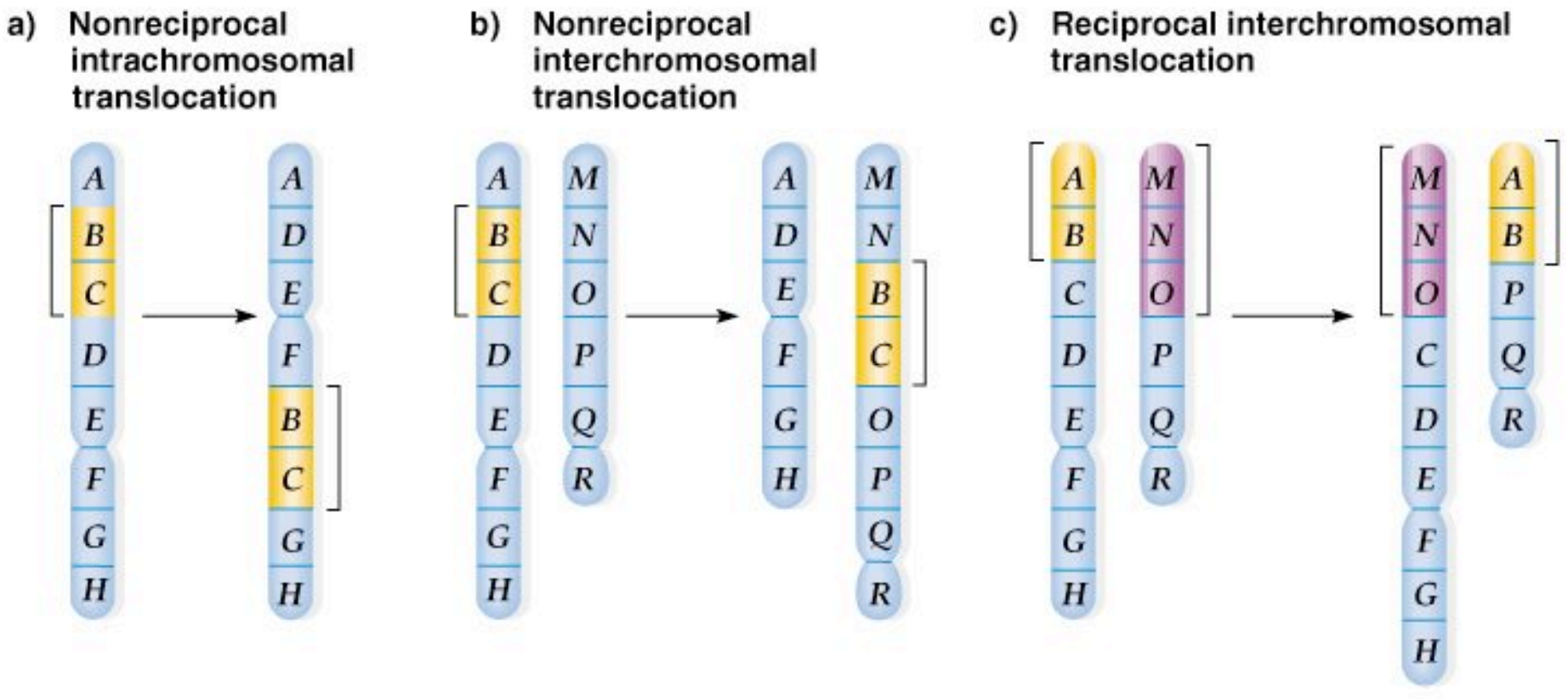
# Variations in Chromosome Structure: Inversions

- In an inversion, the total amount of genetic information stays the same
  - Therefore, the great majority of inversions have no phenotypic consequences
- In rare cases, inversions can alter the phenotype of an individual
  - Break point effect
    - The breaks leading to the inversion occur in a vital gene
  - Position effect
    - A gene is repositioned in a way that alters its gene expression
- About 2% of the human population carries inversions that are detectable with a light microscope
  - Most of these individuals are phenotypically normal
  - However, a few an produce offspring with genetic abnormalities

# Translocations

- A chromosomal translocation occurs when a segment of one chromosome becomes attached to another.
- There are two main types of medically important translocations:
  1. Reciprocal (balanced) Translocations
  2. Robertsonian (unbalanced) Translocations
- Both types of translocations are capable of causing disease in humans.

# Fig. 8.11 Translocations



# Reciprocal Translocations

- In reciprocal translocations two non-homologous chromosomes exchange genetic material
  - Reciprocal translocations arise from two different mechanisms
    - 1. Chromosomal breakage and DNA repair
    - 2. Abnormal crossovers

- Reciprocal translocations lead to a rearrangement of the genetic material
  - not a change in the total amount
  - Thus, they are also called balanced translocations.

# Robertsonian Translocations

- In Robertsonian Translocations the transfer of genetic material occurs in only one direction
- Robertsonian translocations are associated with phenotypic abnormalities or even lethality.
- Example: Familial Down Syndrome
  - In this condition, the majority of chromosome 21 is attached to chromosome 14.
  - The individual would have three copies of genes found on a large segment of chromosome 21
    - Therefore, they exhibit the characteristics of Down syndrome

# Robertsonian Translocation

- This translocation occurs as follows:
  - Breaks occur at the extreme ends of the short arms of two non-homologous acrocentric chromosomes
  - The larger fragments fuse at their centromeic regions to form a single chromosome
  - The small acrocentric fragments are subsequently lost.
  - This type of translocation is the most common type of chromosomal rearrangement in humans.
- Robertsonian translocations are confined to chromosomes 13, 14, 15, 21
  - The acrocentric chromosomes

# Meiosis in Robertsonian Translocation

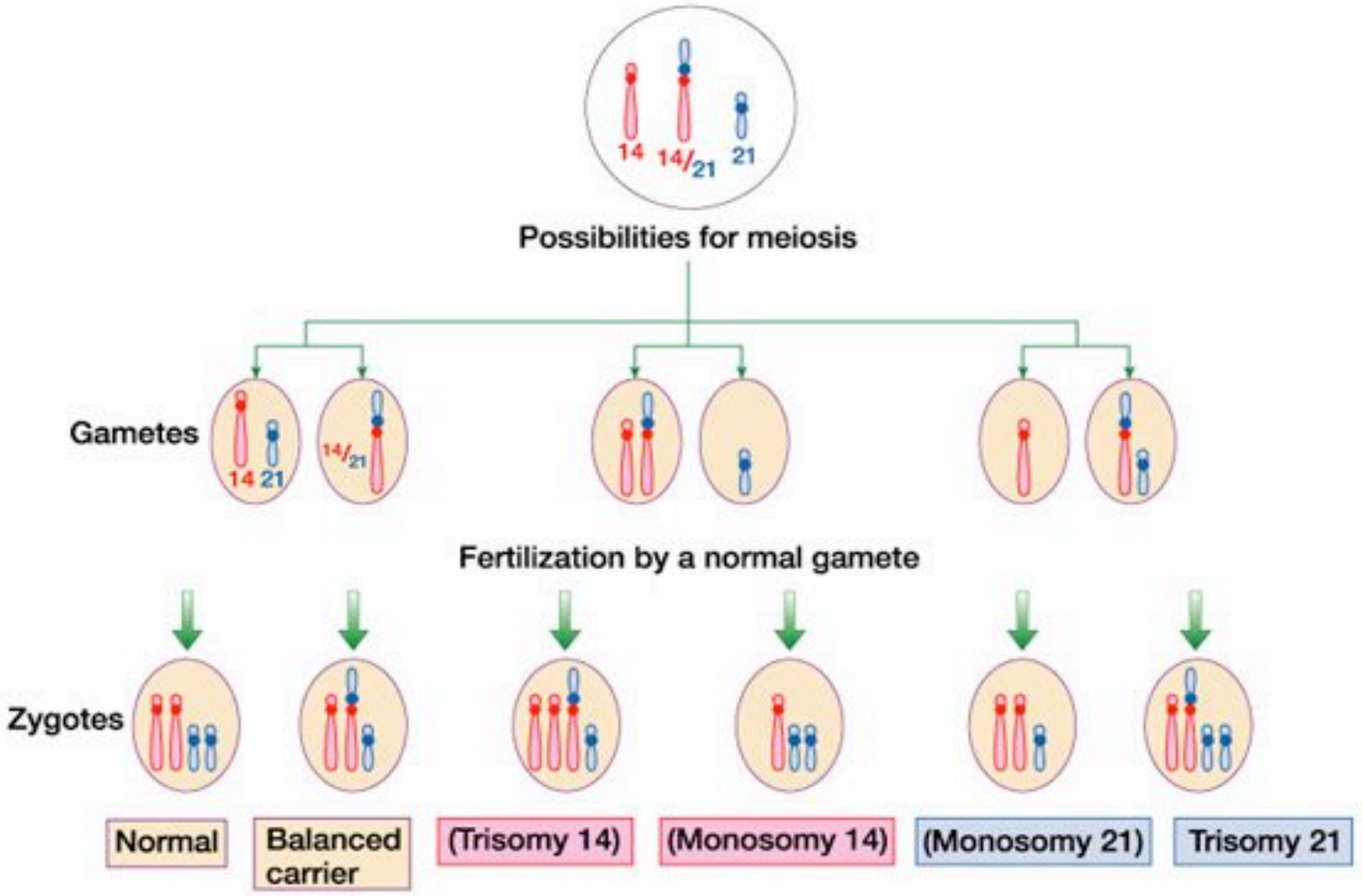



Figure 2-23 Human Molecular Genetics, 3/e. (© Garland Science 2004)

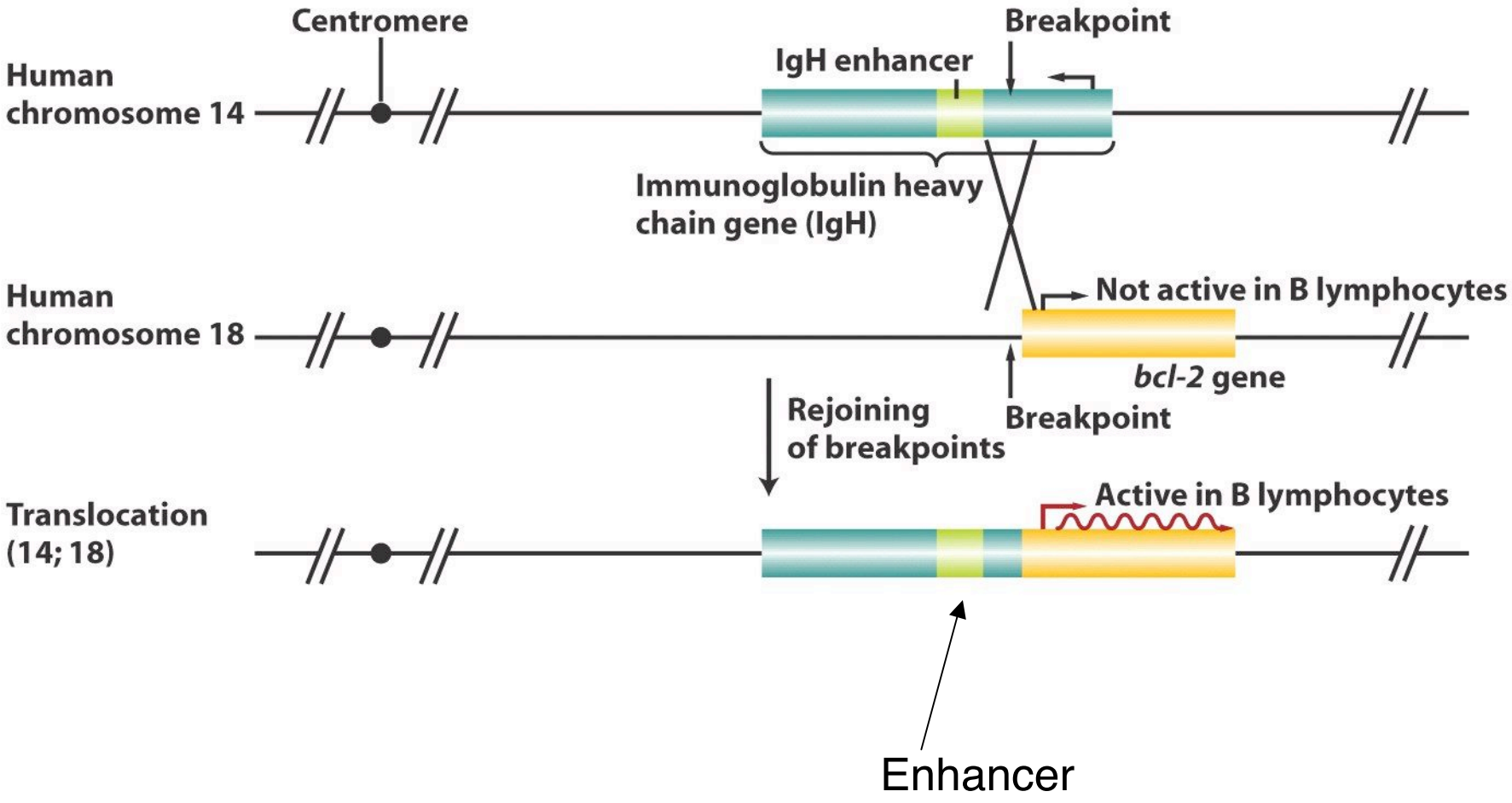
# Chromosomal Mutations and Human Tumors

- Most human malignant tumors have chromosomal mutations.
  - The most common are translocations
  - There is much variation in chromosome abnormalities, however, and they include simple rearrangements to complex changes in chromosome structure and number.
  - Many tumor types show a variety of mutations.
  - Some, however, are associated with specific chromosomal abnormalities.

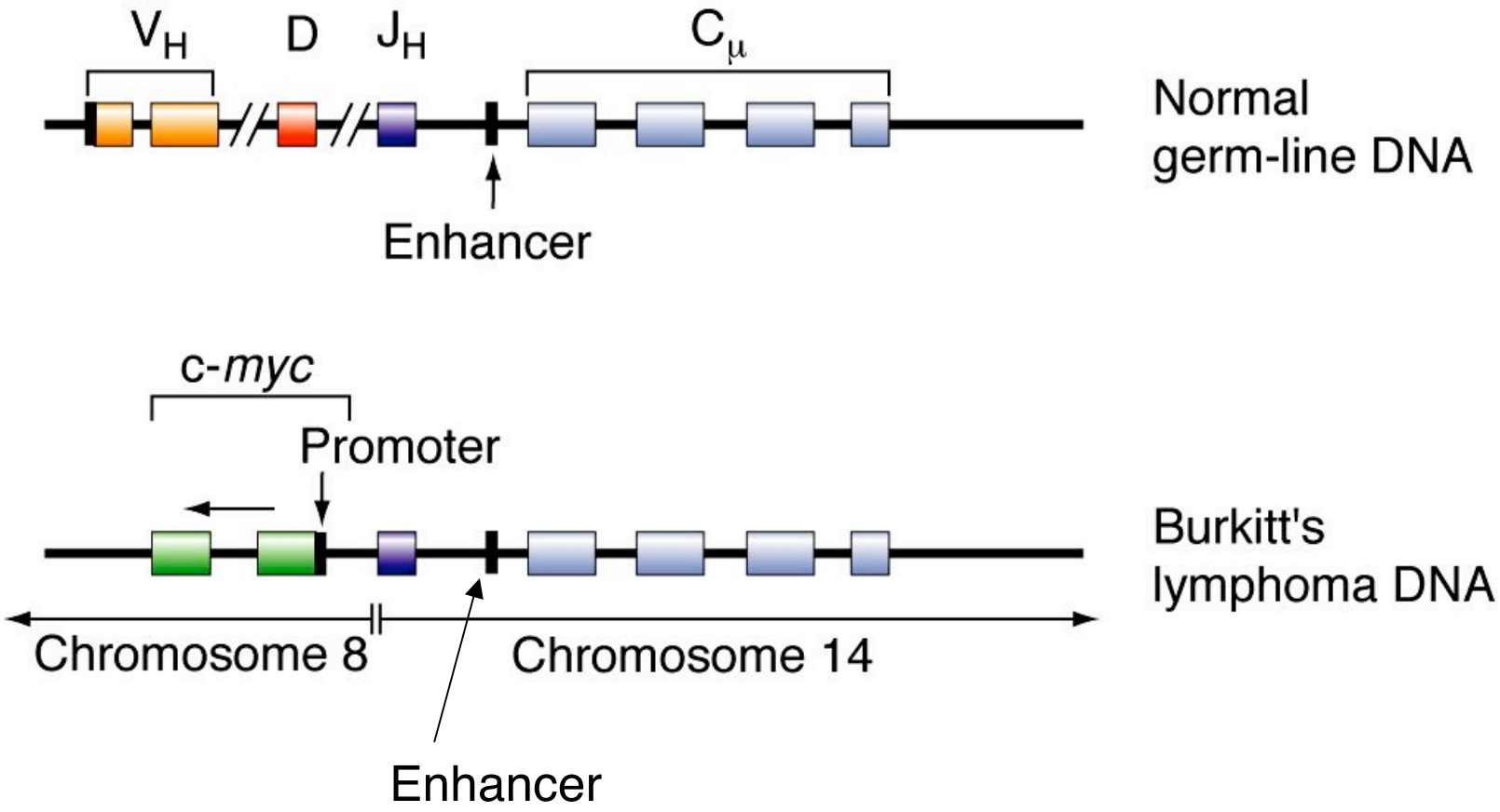
# Translocations

- Usually phenotypically normal; no net loss or gain of material in most cases.
- If breakpoint alters promoter context, gene regulation may be altered
  - e.g.: Burkitt Lymphoma: t(8;14):
- puts the protooncogene *c-myc* next to the immunoglobulin heavy chain locus,
  - resulting in overexpression of *c-myc*
- If breakpoint occurs within a gene, the gene function may be altered
  - e.g.: CML : t(9;22): *Bcr-Abl* fusion product.

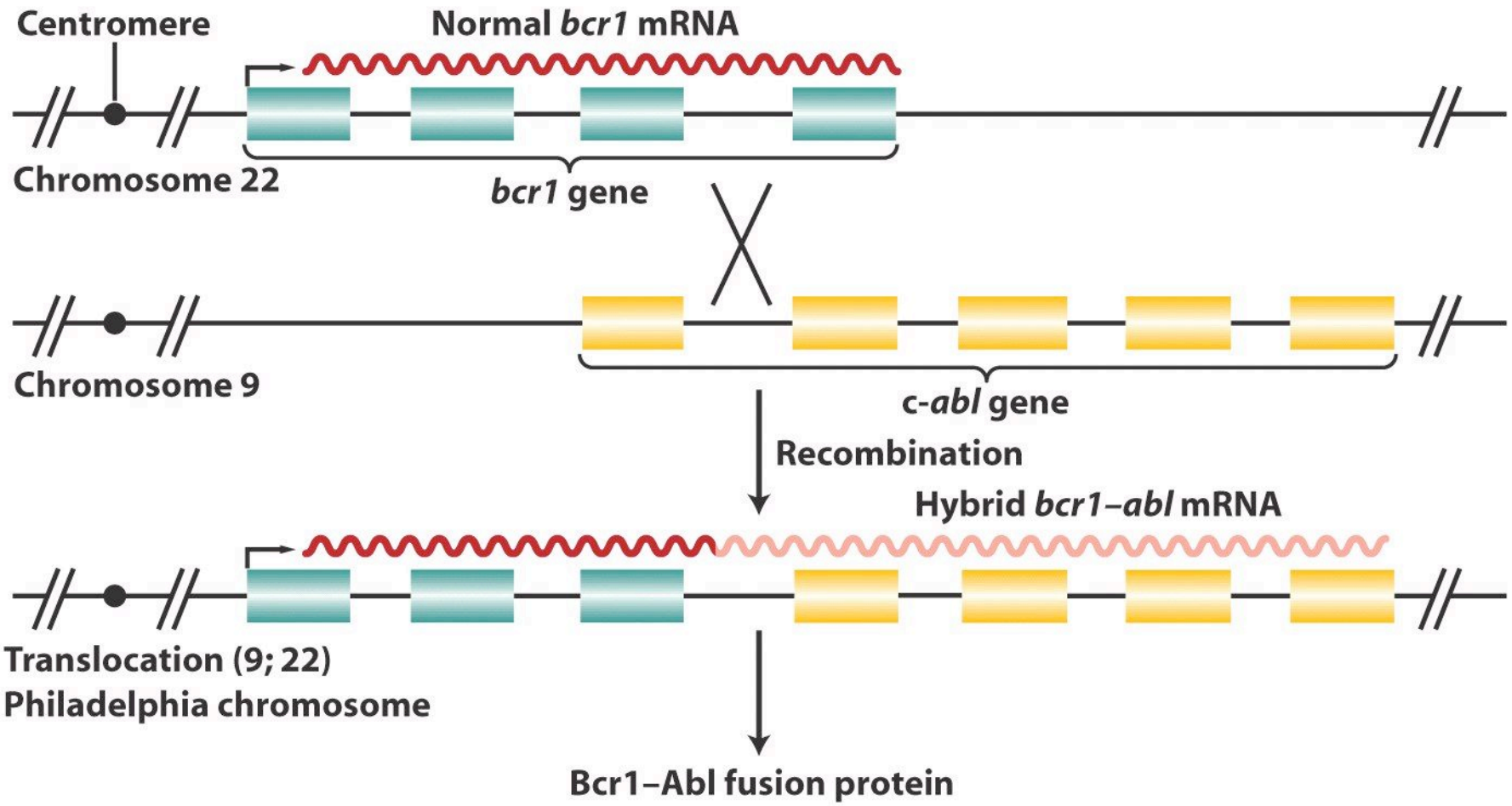
# t(14;18): Folicular Lymphoma



# t(8;14): Burkitt Lymphoma



# t(9;22): Chronic Myelogenous Leukemia



# Homework Problems

- Chapter 8

- # 1, 14a, 17a