

CHAPTER 8
(CHOMOSOME MUTATION: CHANGES IN CHROMOSOME STRUCTURE)
LECTURE NOTES

- I. Background
- A. Chromosomal mutations are processes that result in rearranged chromosome parts, abnormal numbers of individual chromosomes, or abnormal numbers of chromosome sets. The resulting products are also known as chromosomal mutations.
 - B. For our purposes here, we will be talking about alterations in large regions of the chromosome spanning numerous genes
 - C. Abnormalities from chromosomal mutations are frequently due to:
 - 1. change in gene number (balance)
 - 2. change in gene location
 - 3. break internal to a gene
 - D. Can occur in somatic cells, germinal cells, and gametes
 - E. How can you detect a chromosomal mutation? cytogenetics
 - 1. Cytological examination of the actual chromosomes
 - 2. Genetic analysis of inheritance
- II. Physical features of the chromosomes
- A. Size
 - B. Centromere position (appears constricted under microscope)
 - 1. Telocentric (at one end of the chromosome)
 - 2. Acrocentric (off center on the chromosome)
 - 3. Metacentric (in the center of the chromosome)
 - B. Arm length: centromere to the end defines an arm (p = short arm and q = long arm)
 - C. Nucleolar organizer position
 - 1. Nucleoli = intranuclear organelles that contain rRNA (appears as dark spot under microscope)
 - 2. Number of nucleoli ranges from 1 to many per chromosome set
 - 3. Position of nucleolus is next to constriction of the chromosomes called nucleolar organizers which themselves have specific chromosome locations
 - D. Chromomere patterns (beadlike, localized thickening along the chromosomes during prophase)
 - E. Heterochromatin patterns
 - 1. Constitutive heterochromatin is highly condensed chromosomal regions that are for the most part genetically inert and are found in particular chromosomal regions
 - 2. Detected by staining with chemicals (such as Feulgen) that react with DNA as very dense regions of staining
 - F. Banding patterns due to special chromosome staining procedures
 - 1. Specific stains reveal specific bands at specific chromosomal sites
 - a) Quianacrine hydrochloride → Q bands
 - b) Giemsa stain → G bands
 - c) Reversed giemsa → R bands

2. Specialized case of polytene chromosomes in *Drosophila*

E. Karyotype = the entire metaphase chromosome complement of individual

F. Physical characteristics of chromosomes are useful for detecting chromosome mutations such as chromosome rearrangements including deletions, duplications, inversions, and translocations.

III. Deletions (loss of a chromosomal segment)

A B C o D E F → A C o D E F

A. Types

1. Interstitial (Not at the end of the chromosome)

2. Terminal (Near the end of the chromosome)

B. Deletions require two breaks in the chromosome followed by loss of the chromosomal segment and rejoining of the ends.

C. The deleted fragment is acentric (without a centromere) and will be lost upon multiple rounds of cell division.

D. In meiosis I cells heterozygous for the deletion, chromosomes line up normally except that region corresponding to deletion forms a “loop formed to get proper alignment of the homologous chromosomes..

E. Effect of multigenic deletions

1. Homozygous for multigenic deletion = usually lethal.

2. Heterozygous for multigenic deletion = frequently lethal because

a) Unmasking of lethal allele on homologous chromosome without the deletion

b) Upset balance of gene number

F. Detection

1. Genetic

a) Failure of homozygotes to survive

b) Inability of the mutation to revert back to wild type

c) Recombination frequency between the genes flanking the deletion is lower than in the wild type

d) Unmasking of a recessive allele present on the homologous chromosome without the deletion (pseudodominance of the recessive allele)

2. Cytological

a) Deletion loop in meiosis

b) Change in banding patterns

G. Using deletions to map genes

1. Deletion mapping

a) Cross a new recessive mutant with a set of deletion mutants of known map location. The new mutation will show pseudodominance when heterozygous for the deletion that contains the region to which the new mutation maps. See figure 8-8 in text.

b) Cross a new mutant suspected of containing a deletion with a set of recessive mutants of known map location. Look for the pseudodominance effect which indicated that your putative deletion is in the same area as the gene that is showing pseudodominance

2. In situ hybridization

Add a radioactively labeled gene of interest to a chromosome deletion set and look for the presence or absence of radioactivity for each deletion. The chromosome deletions that do not hybridize to the radioactive gene probe are deleted for the region that contains the gene of interest.

IV. Duplications (presence of two copies of a chromosomal region)

A B C o D E F → A B C B C o D E F

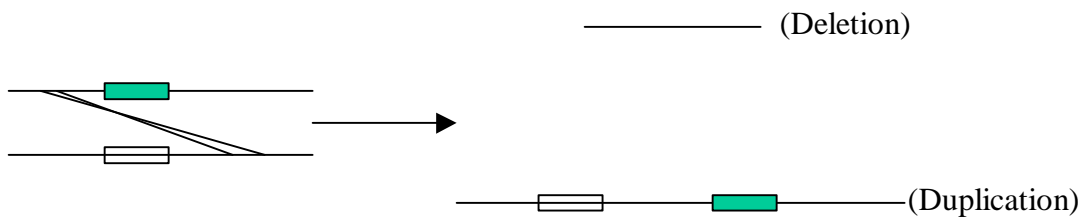
OR

A B C o D E F → A B C C B o D E F

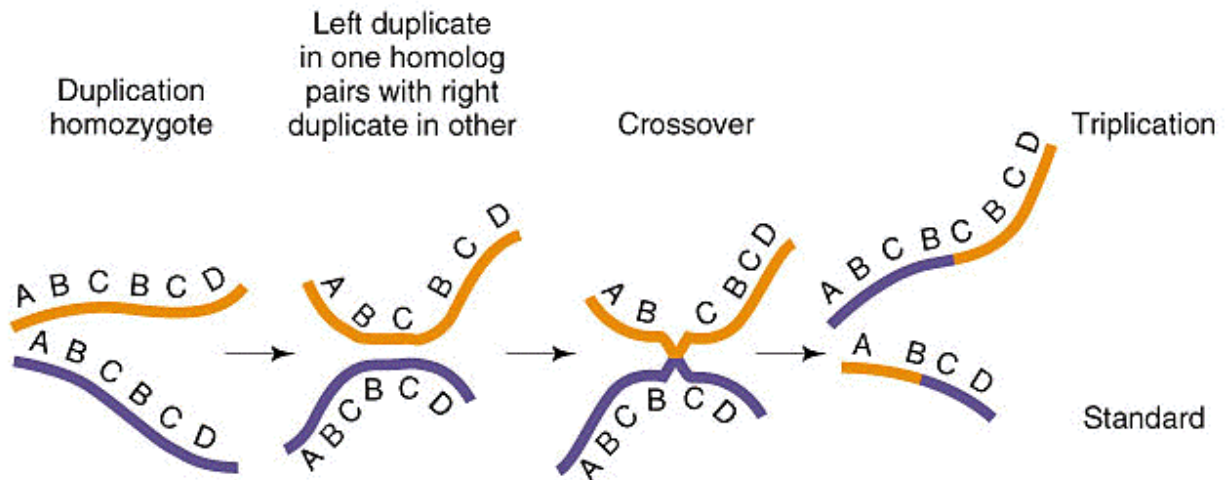
A. Types

1. tandem (adjacent to each other in same order)
2. reverse tandem (adjacent to each other in reverse order)
3. nontandem (at a different chromosomal location)

B. Tandem duplications can occur due to unequal crossing over where homologous chromosomes pair inaccurately during meiosis I



C. Nontandem duplications may result from crossing over during meiosis within segments of the chromosome that contain inversions or translocations (see later).
 D. In meiosis I cells heterozygous for the duplication, chromosomes line up normally except that region corresponding to duplication forms a “loop” formed to get proper alignment of the homologous chromosomes. Also, asymmetric pairing within the duplicated region may occur during meiosis I, leading to unequal crossover.



(from An Introduction to Genetic Analysis, 6th ed. by Griffiths et al. (W. H. Freeman and Company))

E. Effect of duplications

1. Duplications are rare.
2. Heterozygous for duplication = can be lethal because of imbalance generated by extra copies of the duplicated region.
3. Homozygous for duplications is unknown in medical genetics.

F. Detection is difficult. Cytology is the main tool (change in bands and duplication loop in meiosis I)

G. Duplications have been proposed to be important for evolution because they provide an extra copy of genes that can then undergo mutation while still leaving the original gene unaffected.

V. Inversions (flipping of chromosomal segment relative to the rest of the chromosome)

A B C D E o F G H → A D C B E o F G H

OR

A B C o D E F → A E D o C B F

A. Types

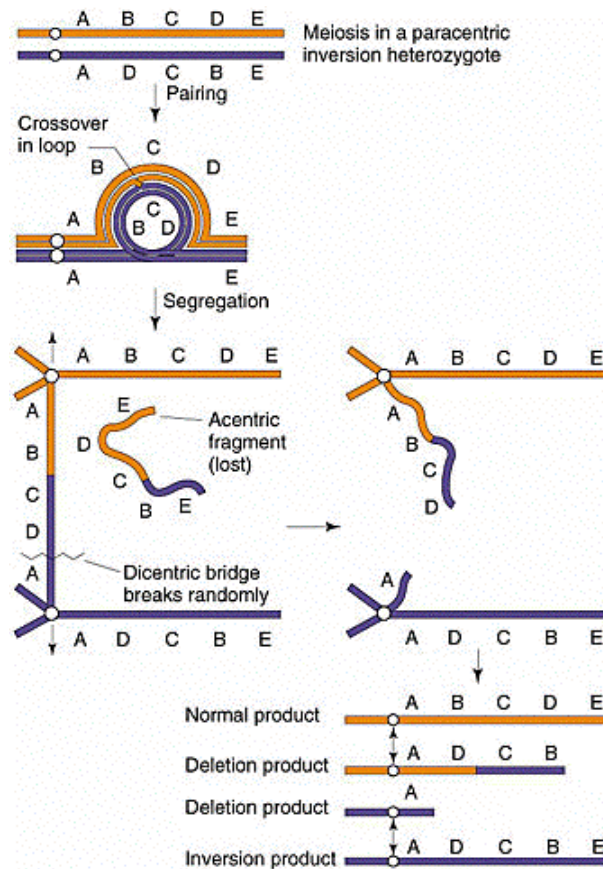
1. Paracentric – centromere outside the inversion
2. Pericentric – centromere inside the inversion

B. Inversions require two breaks in the chromosome followed by a 180° rotation of the chromosomal segment and rejoining of the ends.

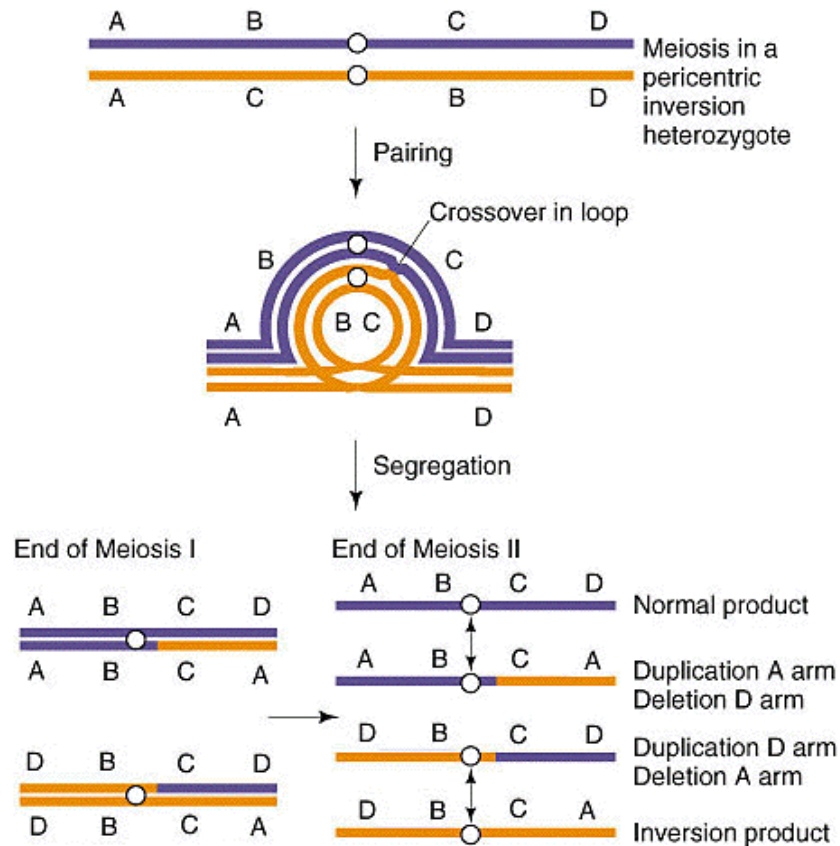
C. In meiosis I cells heterozygous for the inversion, inversion loop is formed to get proper alignment of the homologous chromosomes.

1. Paracentric

(from An Introduction to Genetic Analysis, 6th ed. by Griffiths et al. (W. H. Freeman and Company))



2. Pericentric



(from An Introduction to Genetic Analysis, 6th ed. by Griffiths et al. (W. H. Freeman and Company))

D. In meiosis I cells **homozygous** for the inversion, crossover is normal but linkage map shows inverted gene order.

E. Effects of inversions are negligible because there is no change in the genetic material. However, those heterozygous for inversions produce abnormal meiotic crossover products and possibly abnormal progeny (if they survive at all).

F. Detection

1. Genetic – recombinant progeny are usually not recovered from heterozygotes
2. Cytological
 - a) If the duplication is pericentric, the arm lengths change.
 - b) Change in the banding pattern
 - c) Dicentric bridge in meiosis for paracentric inversion

IV. Translocations (movement of a chromosomal segment from one location to another)

A B C o D E and G H I o J K

→

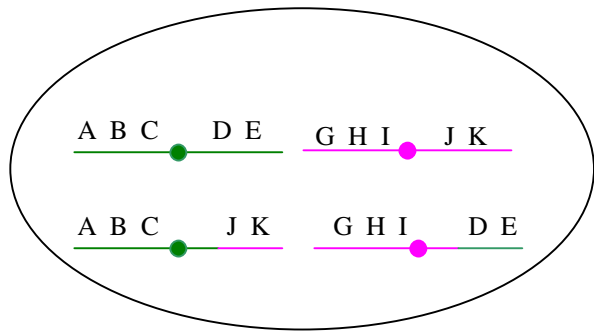
A B C o J K and G H I o D E

A. Types

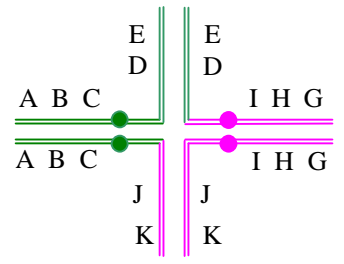
1. Reciprocal (exchange of segments)
2. Nonreciprocal (1 segment moves to a new location without an exchange)

B. Reciprocal translocations require two breaks in two different chromosomes followed by rejoining of the ends.

C. In meiosis I cells heterozygous for the deletion, cross conformation forms to get proper alignment of the homologous chromosomes. Showing only meiosis I on the next page:



Heterozygous for translocation

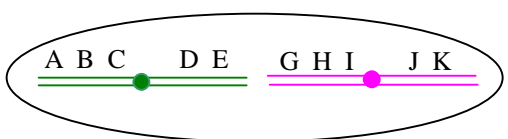


Lining up during Meiosis I

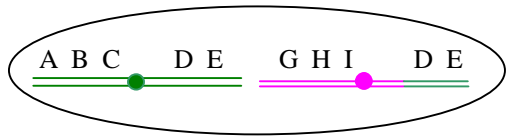
Alternate Segregation

OR

Adjacent-1 Segregation



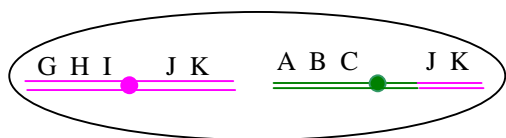
wild type



Deleted for JK
Duplicated for DE



translocated



Deleted for DE
Duplicated for JK

(In most cases, these gametes form nonviable progeny even when mated with wild type.)

D. Effect of translocations

1. Semisterility due to adjacent segregation in meiosis
2. Position effects: altered expression of a gene when it is moved to a new location

E. Detection

1. Genetic
 - a) Semisterility
 - b) Apparent linkage of genes on separate chromosomes
 - c) Position effects
2. Cytological
 - a) Can change the location of the centromere
 - b) Change in the size of the chromosome
 - c) Cross formation in meiosis I