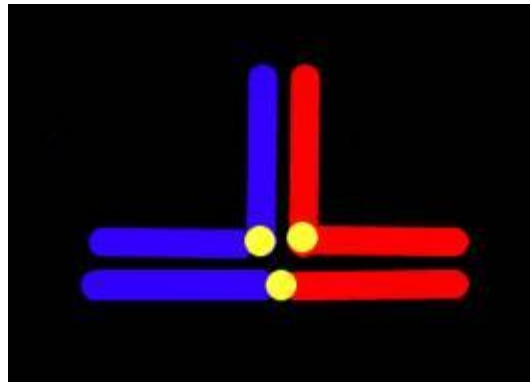# Chromosome rearrangements

Chromosome rearrangements

Chromosome rearrangements are caused by **breakage of DNA double helices** in the genome at two different locations, followed by a **rejoining of the broken ends** to produce a new chromosomal arrangement of genes, different from the gene order of the chromosomes before they were broken.

Most common chromosome rearrangements are

(i) deletions

(ii) duplications

imbalanced - change the gene dosage of a part of the affected chromosomes, similar to aneuploidy for whole chromosomes (the loss of one copy or the addition of an extra copy of a segment of a chromosome can disrupt normal gene balance)

(iii) inversions

(iv) translocations

balanced - change the chromosomal gene order but do not remove or duplicate any of the DNA of the chromosomes

Chromosome rearrangements: points to remember

- each chromosome is a single double-stranded DNA molecule (DNA helix)

- the first event is the generation of two or more **double-strand breaks (DSBs)** in the chromosomes

- DSBs are potentially lethal, unless they are repaired

- repair systems in the cell correct the DSBs by joining broken ends back together

- if the two ends of the same break are rejoined >> the original DNA order restored, **if ends of two different breaks are joined together (= mis-repair of DNA damage) >> chromosome rearrangement**

- segment of DNA lost or duplicated in the rearrangement cannot be "too large" (gene balance); the larger the segment of a chromosome lost or duplicated, the more likely will it cause phenotypic abnormalities
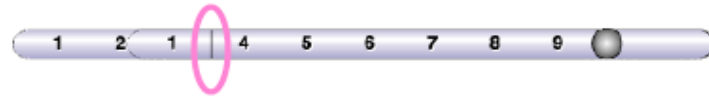
Chromosome rearrangements – the role of repeats

In organisms with repetitive DNA, homologous repetitive segments **within one chromosome** or **on different chromosomes** can act as sites for illegitimate crossing-over.

Deletions, duplications, inversions, and translocations can all be produced by such crossing-over.
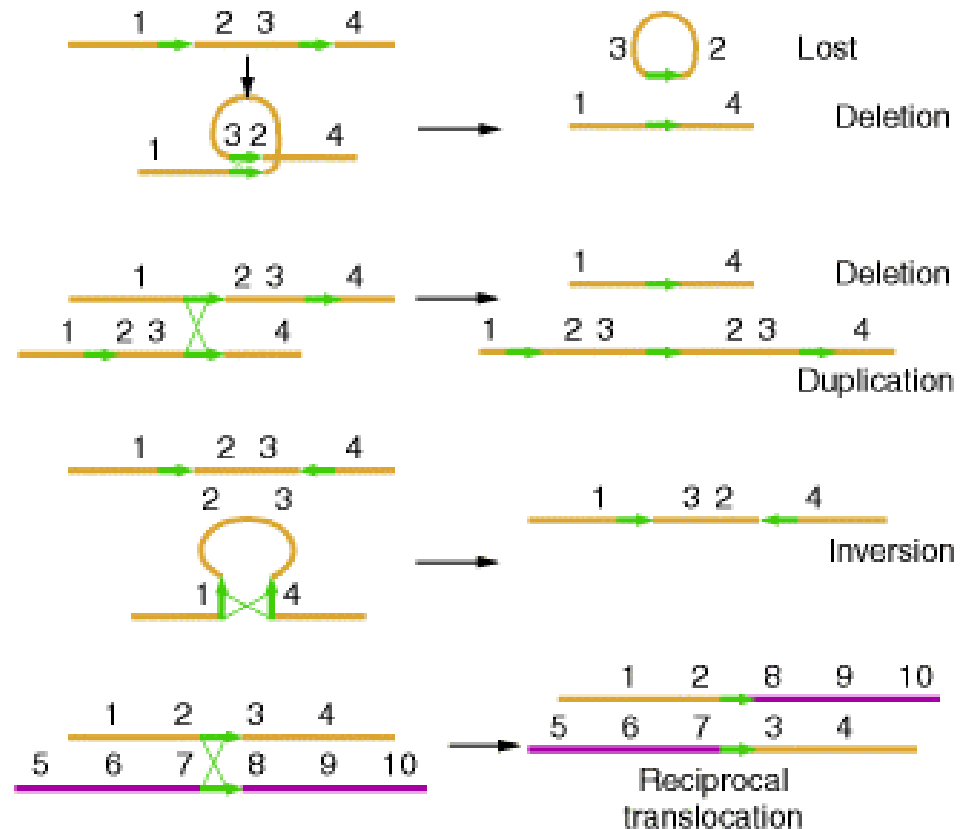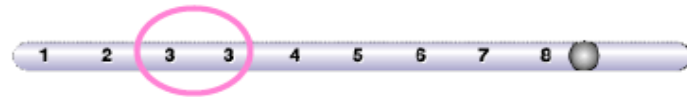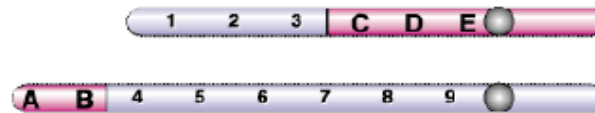
Chromosome rearrangements

Deletions

Duplications
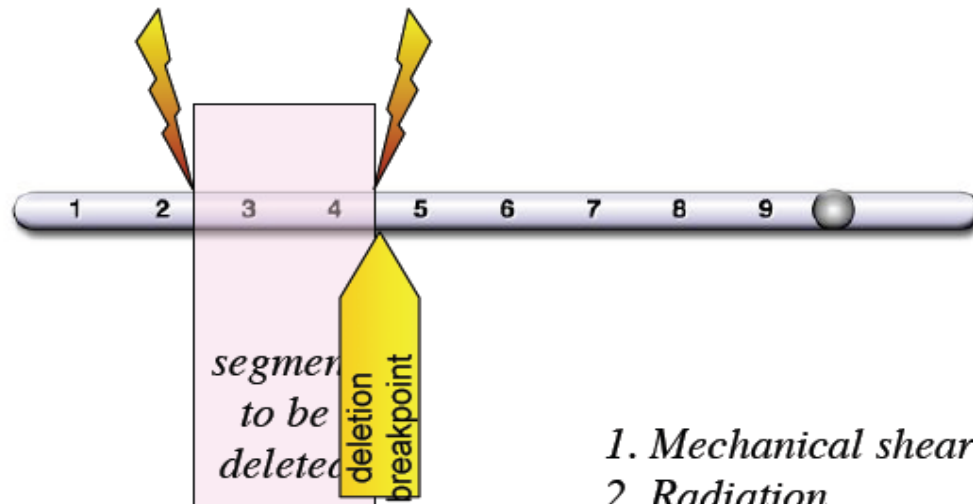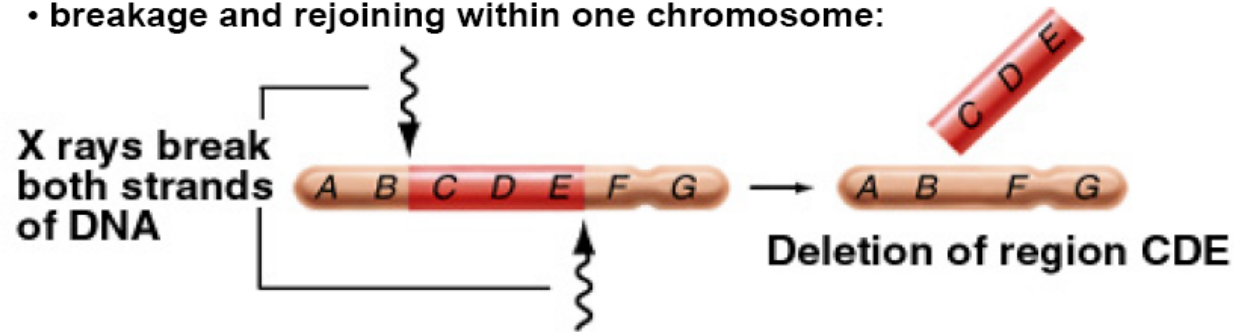
Inversions

Translocations

Deletion formation by breakage and rejoining

= deficiencies = losses of chromosome segments

• can occur **terminally** or **internally**, e. g. caused by…
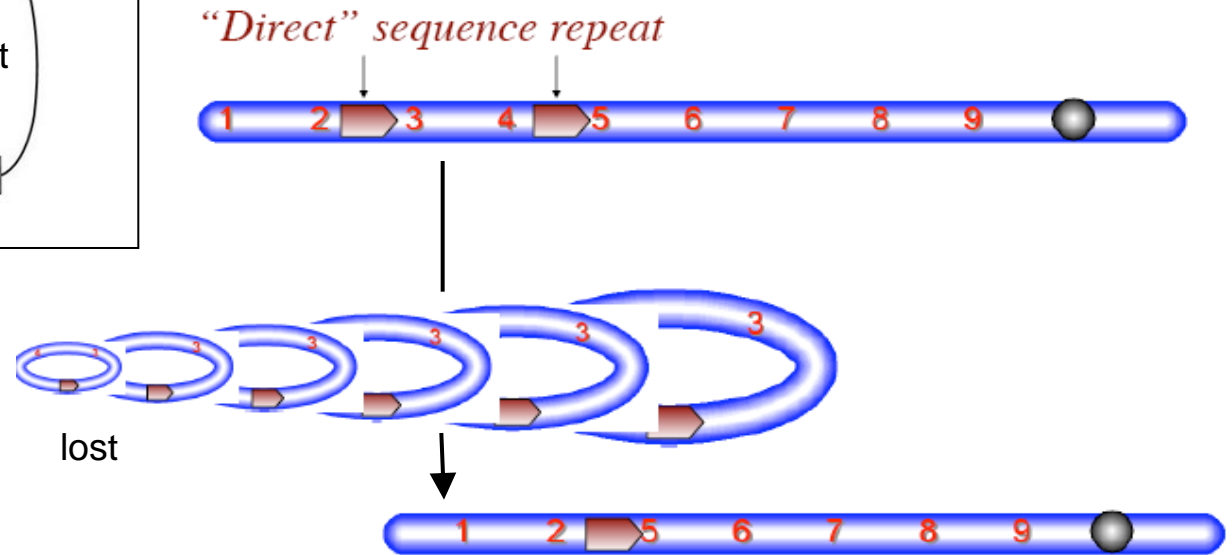
     • breakage and rejoining within one chromosome:

X rays break both strands of DNA

Deletion of region CDE

segment to be deleted

deletion breakpoint

1. Mechanical shear
2. Radiation
3. Transposable elements

Deletion formation by intra-chromosomal crossover

lost

deletion

another example…

"Direct" sequence repeat

1 2 3 4 5 6 7 8 9

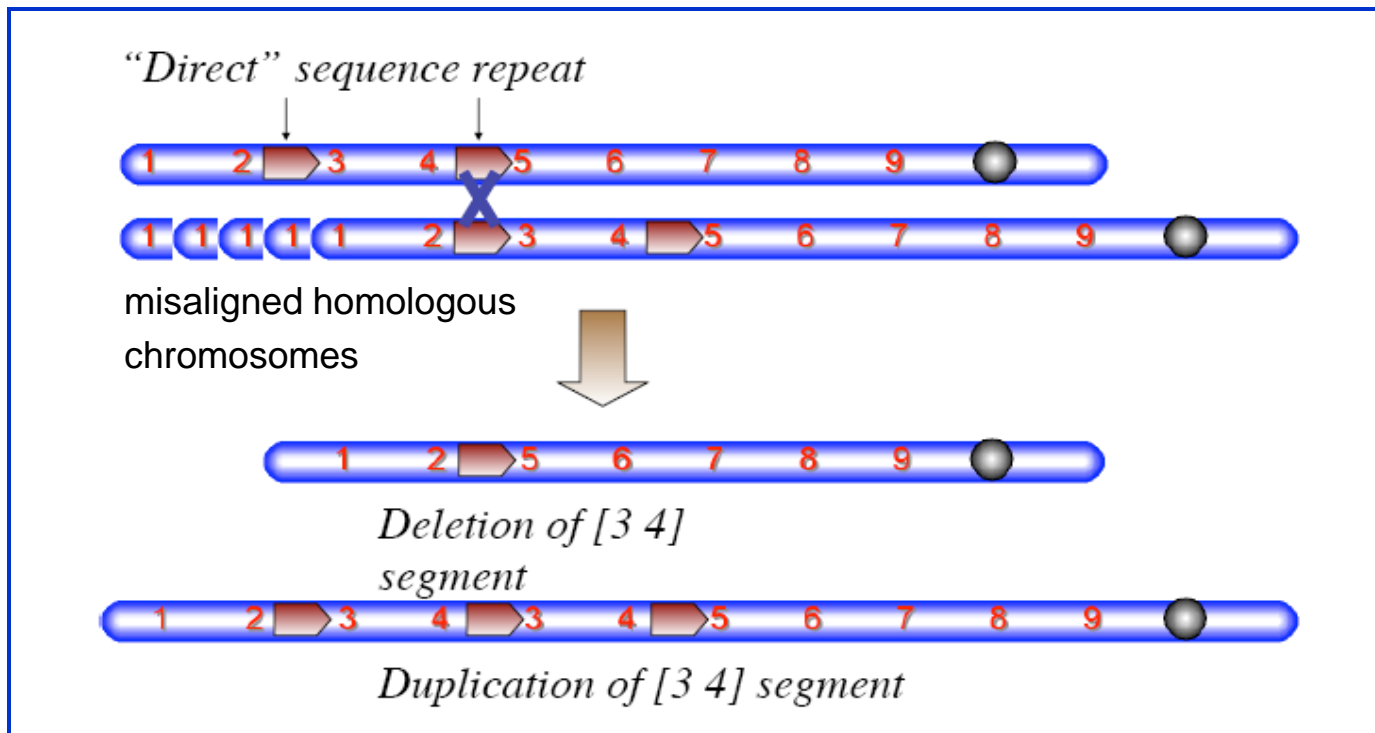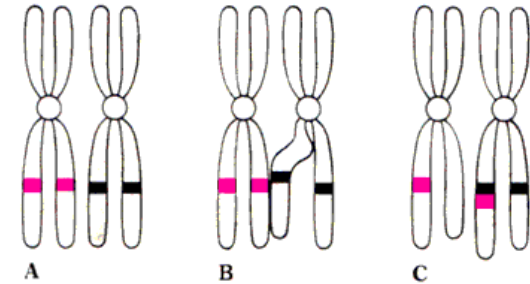lost
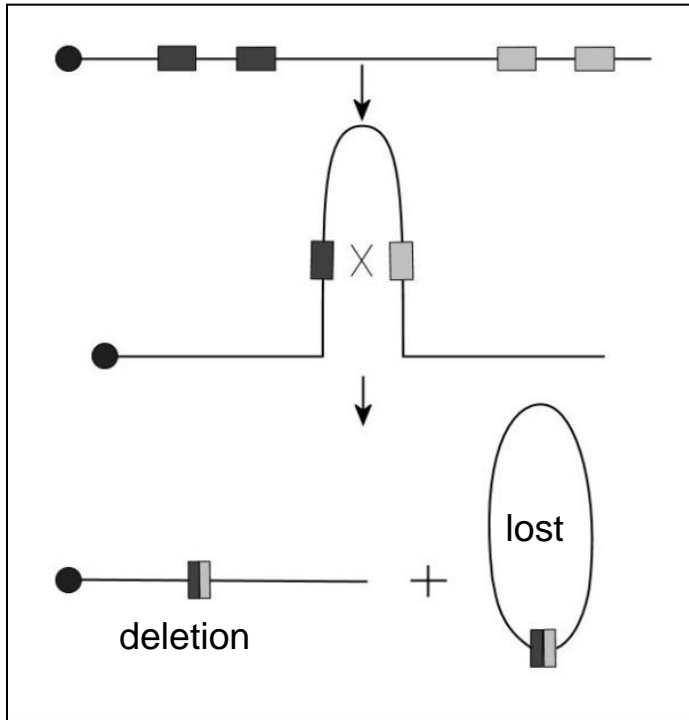
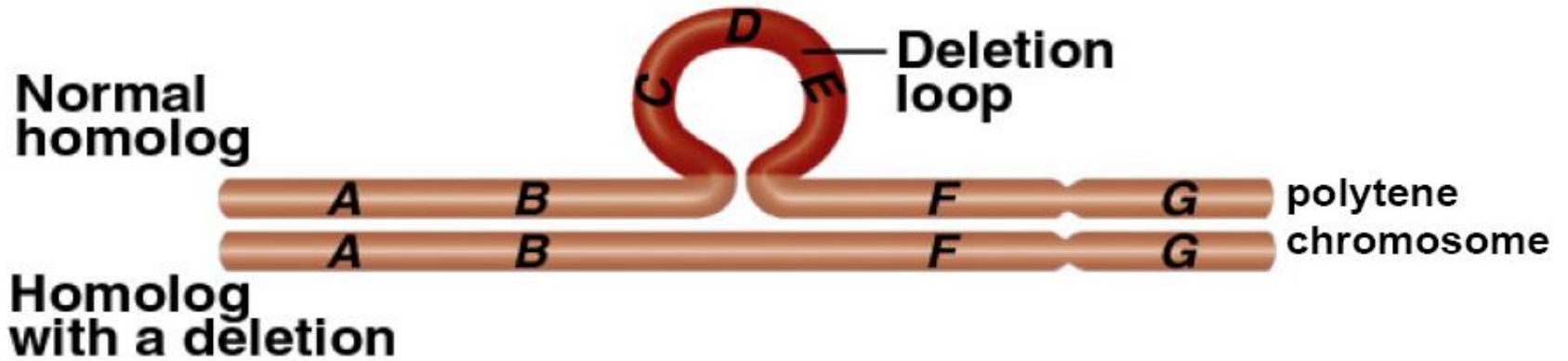Deletion with one copy of direct-repeat sequence

Deletion (and duplication) formation by unequal cross-over

Sometimes during meiosis two chromatids from homologous chromosomes **(A)** are misaligned during a cross-over event **(B)** as a result, one chromatid gained a duplicated region and the another lost a deleted region **(C)**. The duplication as well as the deletion are inherited by resulting gametes.
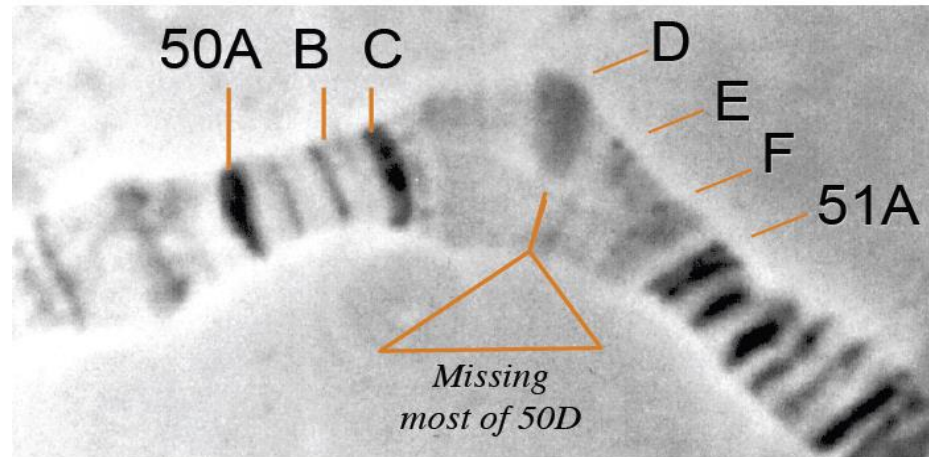

A   B   C

"Direct" sequence repeat

misaligned homologous chromosomes

Deletion of [3 4] segment

Duplication of [3 4] segment

How deletions can be identified

by finding a visible change in chromosome structure:

Normal homolog

Deletion loop

polytene chromosome

Homolog with a deletion

polytene chromosomes

Drosophila deletion heterozygote

50A B C   D
            E
             F
            51A

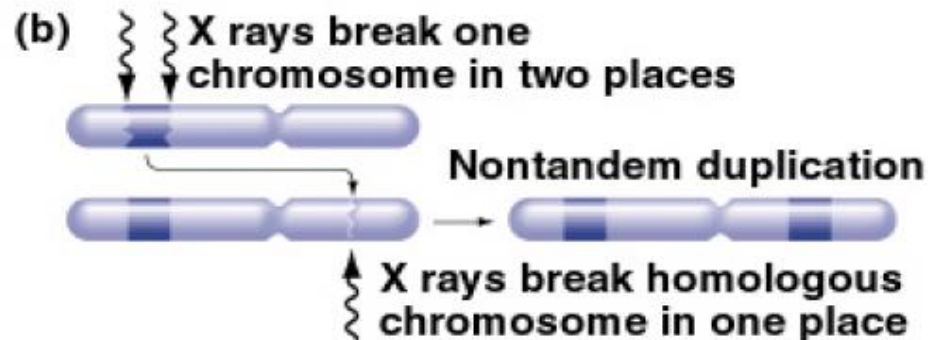*Missing most of 50D*

Duplications: polyploidy

autopolyploidy vs. allopolyploidy
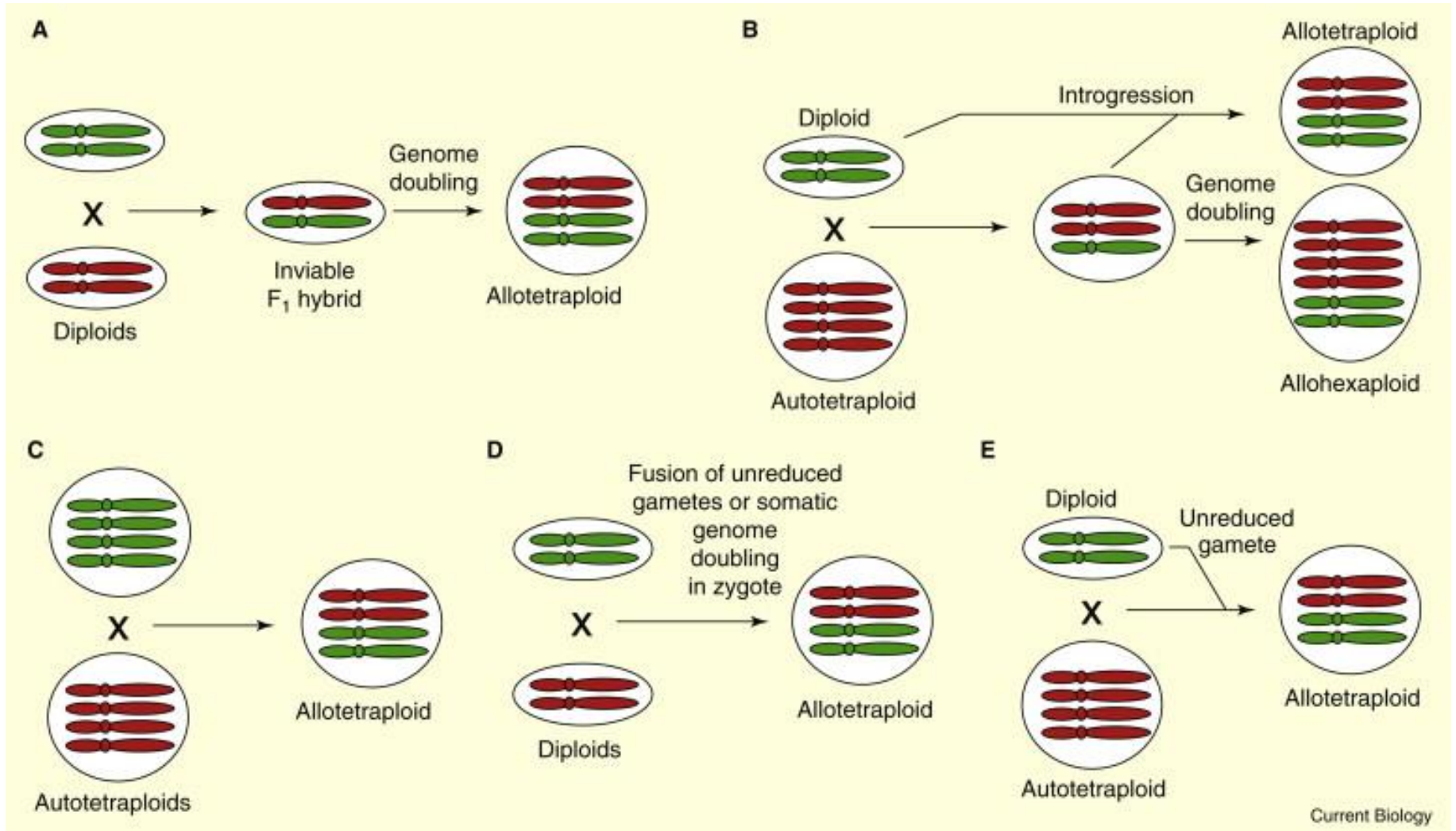
Segmental duplications

(a) Tandem duplication

Normal chromosome A B C D E F G

Same order A B C B C D E F G

Reverse order A B C C B D E F G

Nontandem (dispersed) duplications

Same order A B C D E F B C G

Reverse order A B C D E F C B G

(b) X rays break one chromosome in two places

Nontandem duplication

X rays break homologous chromosome in one place
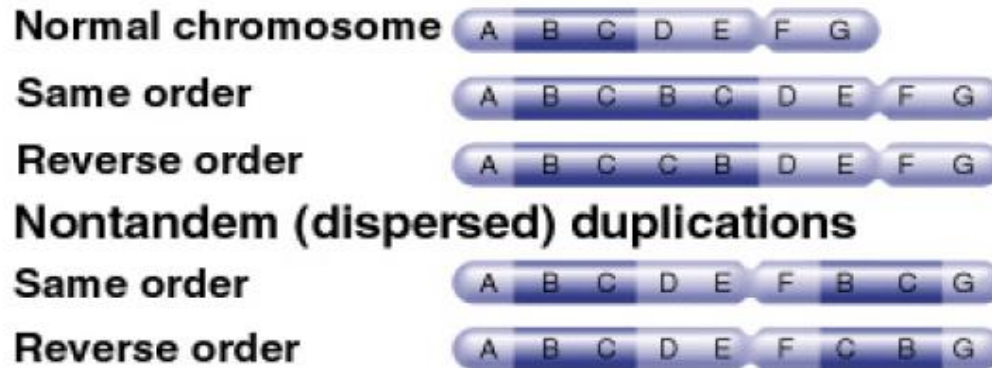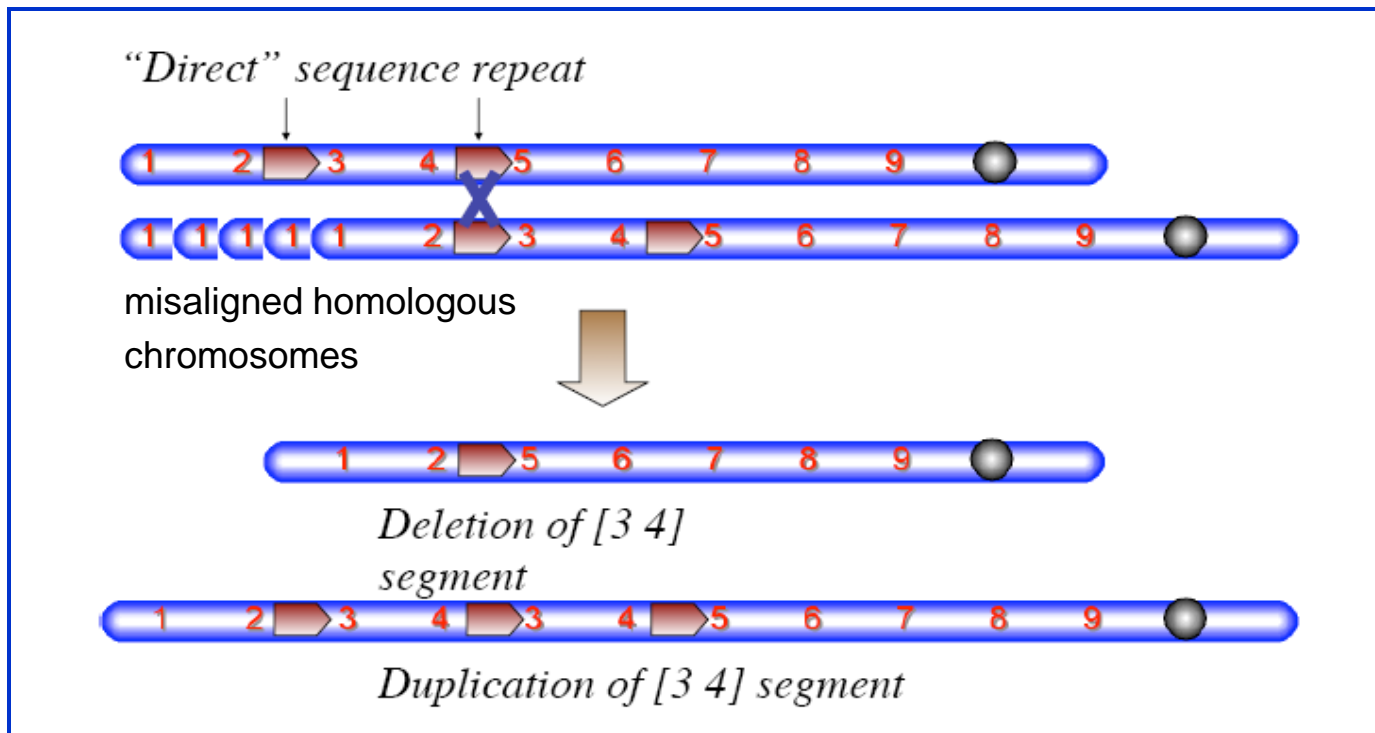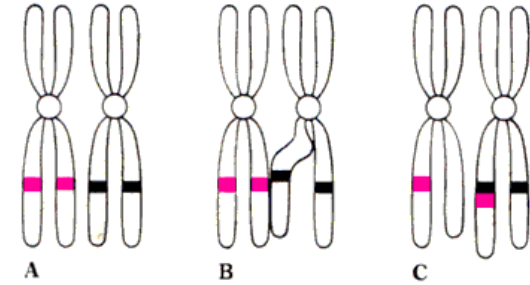
Duplication (and deletion) formation by unequal cross-over

- common mechanism of duplications

Sometimes during meiosis two chromatids from homologous chromosomes **(A)** are misaligned during a cross-over event **(B)** as a result, one chromatid gained a duplicated region and the another lost a deleted region **(C)**. The duplication as well as the deletion are inherited by resulting gametes.

A   B   C

"Direct" sequence repeat

1 2 3 4 5 6 7 8 9

1 1 1 1 1 2 3 4 5 6 7 8 9

misaligned homologous chromosomes

1 2 5 6 7 8 9

Deletion of [3 4] segment

1 2 3 4 3 4 5 6 7 8 9

Duplication of [3 4] segment

Consequences of duplications

- most duplications have no phenotypic consequence

- sometimes effects can be seen due to increased gene dosage

- play a very important role in evolution:
    - increase gene number
    - evolution of new genes (paralogs!)

1970 **Susomo Ohno** – "Evolution by Gene Duplication"

Gene duplication produces a reservoir of genes from which to evolve new ones. Why reinvent the wheel from scratch?

- evolution of RNA genes

- in particular rRNA genes (rDNA)

- 5-10 copies/bacterial genome

- c. 130 copies/Drosophila genome

- *Xenopus* c. 400 copies/genome (but the oocyte may have 1500 micronuclei, each with an NOR, it is c. 600,000 copies of rDNA)
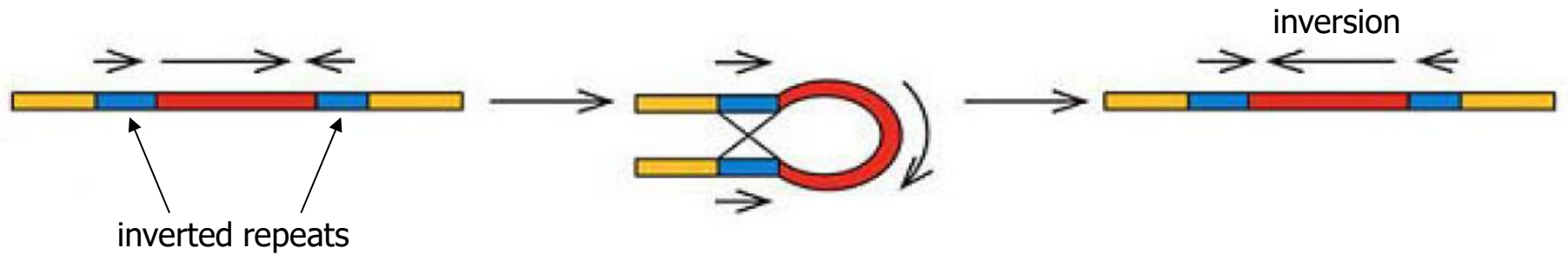
Inversions

Inversions as balanced rearrangements are generally viable and show no particular abnormalities at the phenotypic level. Many inversions can be made homozygous.

Inversion heterozygote - cells that contain one normal haploid chromosome set plus one set carrying the inversion. Microscopic observation of meioses in inversion heterozygotes reveals an **inversion loop**.
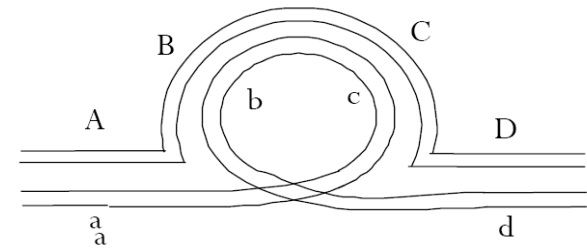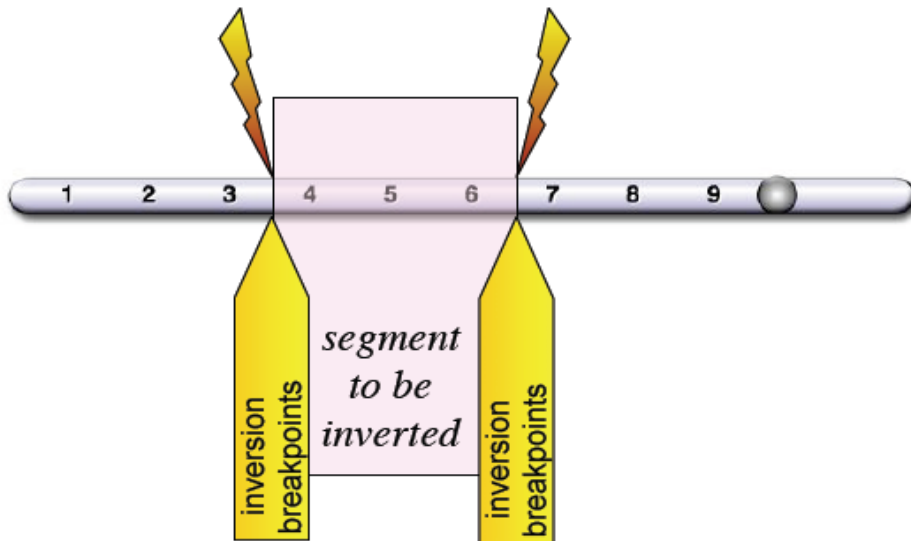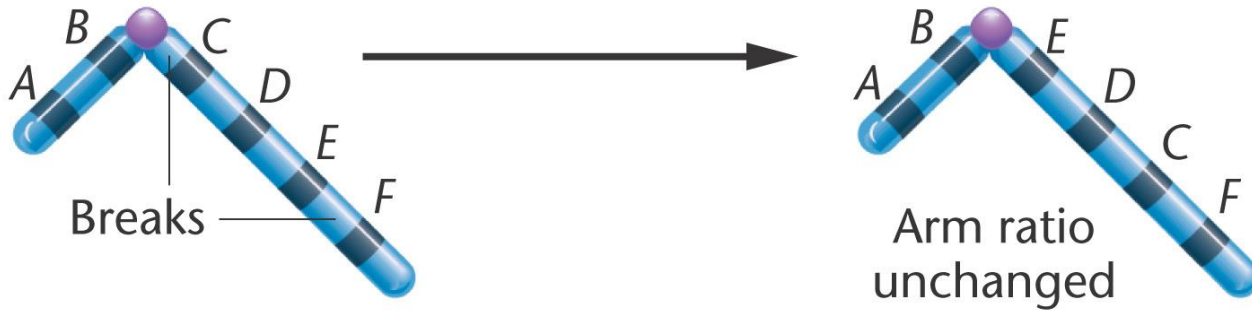
meiotic inversion loop
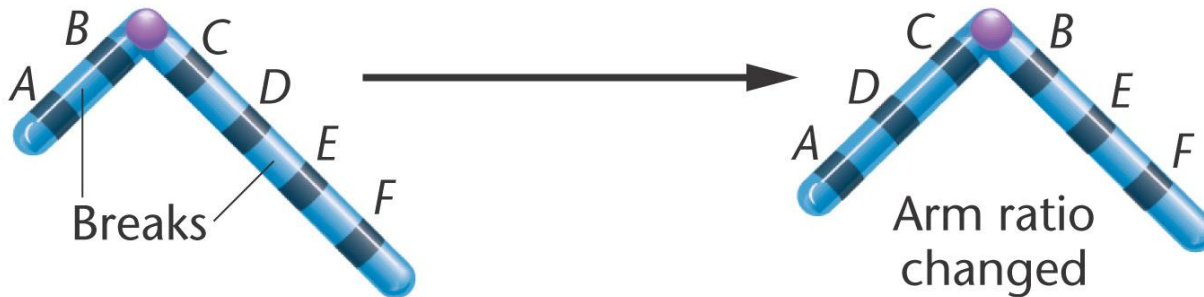
Inversion formation by intra-chromosomal crossover

inverted repeats

inversion

Two types of inversions

Paracentric inversion

Breaks

Arm ratio unchanged

Pericentric inversion

Breaks
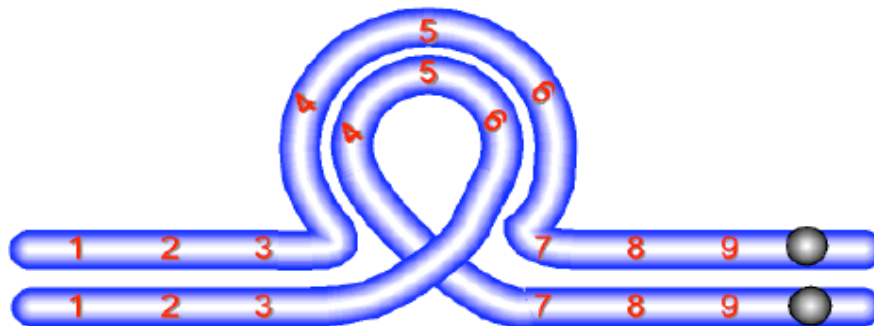
Arm ratio changed

mechanism of inversion formation: breakage and rejoining

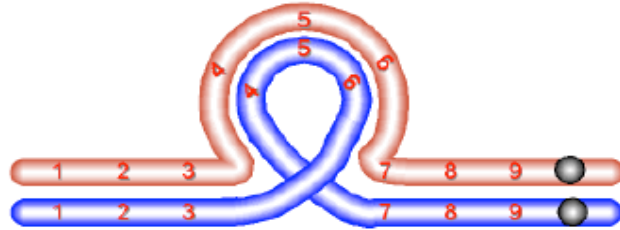# How the chromosomes pair in an inversion heterozygote?

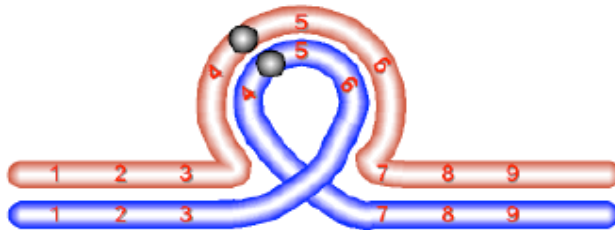**(paracentric) inversion heterozygote**
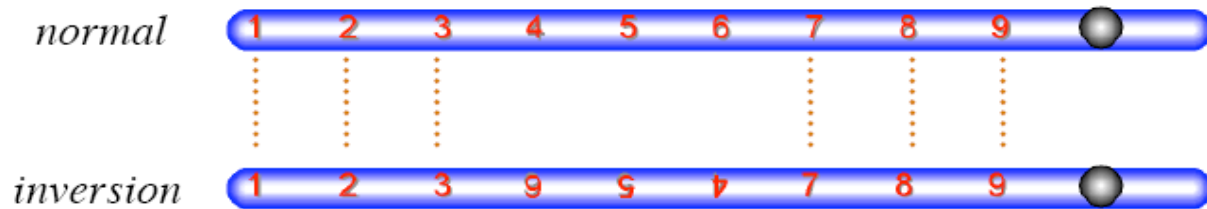
by forming an inversion loop...

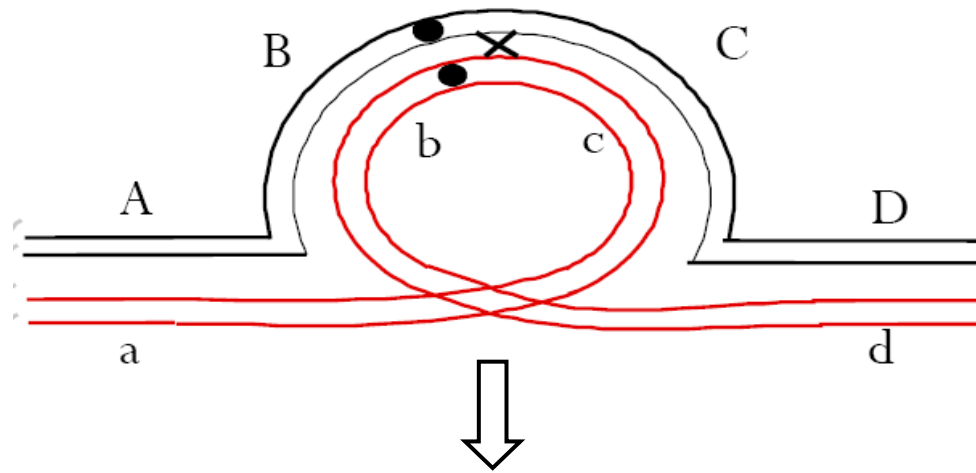# Inversion loops in para- and pericentric inversion heterozygotes

paracentric inversion
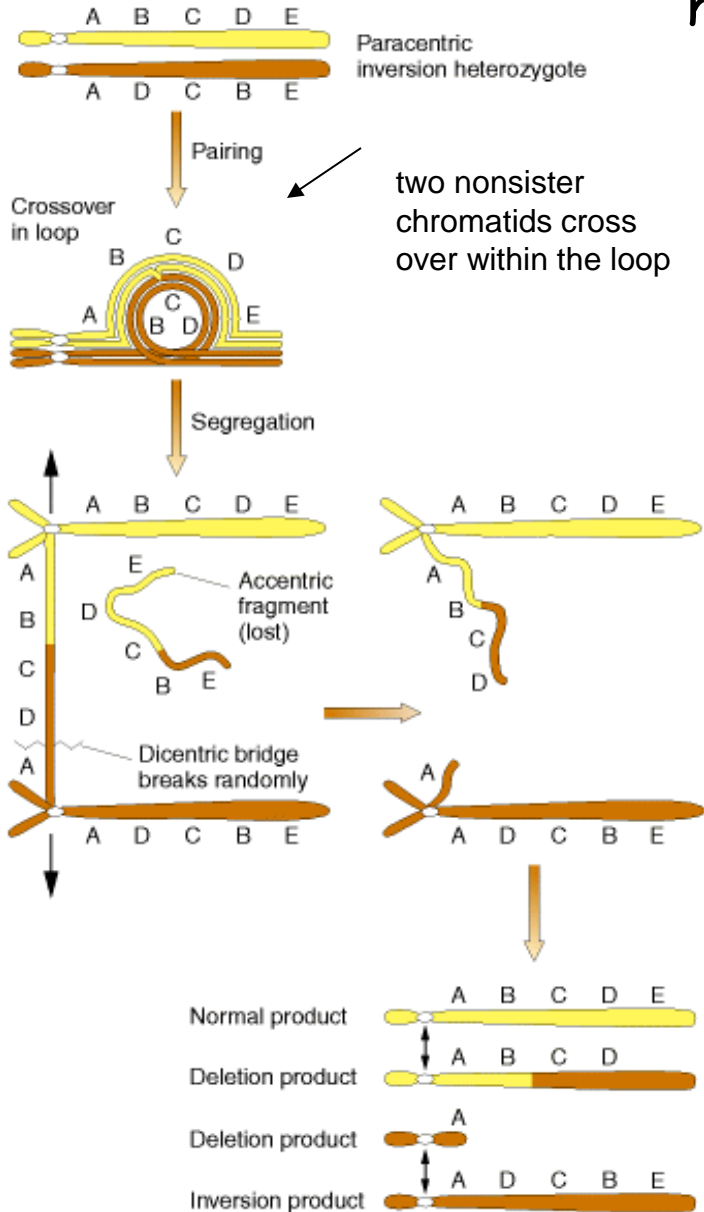
pericentric inversion

When no recombination occurs, 50% of gametes have inversion. Next two slides show what happen if a recombination event does occur in the inversion loop...

A crossover within the inversion loop of a heterozygote for a pericentric inversion

A   B   C   D   wild type

A   B   c   a   duplication/deletion (gametes/zygotes not viable)

a   c   b   d   inversion

d   b   C   D   duplication/deletion (gametes/zygotes not viable)

A crossover within the inversion loop of a heterozygote for a paracentric inversion

Paracentric inversion heterozygote

Pairing

two nonsister chromatids cross over within the loop

Crossover in loop

Segregation

Accentric fragment (lost)

Dicentric bridge breaks randomly

Normal product

Deletion product

Deletion product

Inversion product

Crossing-over within the inversion loop connects homologous centromeres in a **dicentric bridge** while also producing an **acentric fragment** - one without a centromere.

Anaphase I
- the **acentric fragment** cannot align itself and it is lost
- tension eventually breaks the **dicentric bridge**, forming two chromosomes with terminal deletions

Gametes containing deleted chromosomes may be inviable, but, even if viable, the zygotes that they eventually form will probably be inviable. Crossing-over generates here lethal products.

Inversions affect recombination in another way, too. Inversion heterozygotes often have mechanical pairing problems in the region of the inversion, which reduces the opportunity for crossing-over in the region. Consequences for speciation.

Inversions and recombination: evolutionary significance

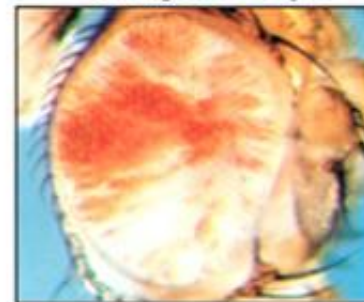Can be "adaptive" when it stabilizes a superior combination of alleles on a chromosome (examples seen in *Drosophila)*
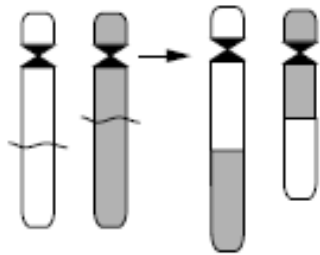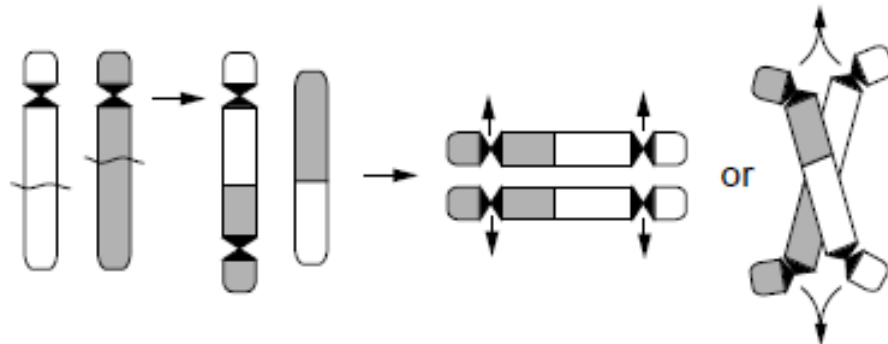
Position-effect variegation
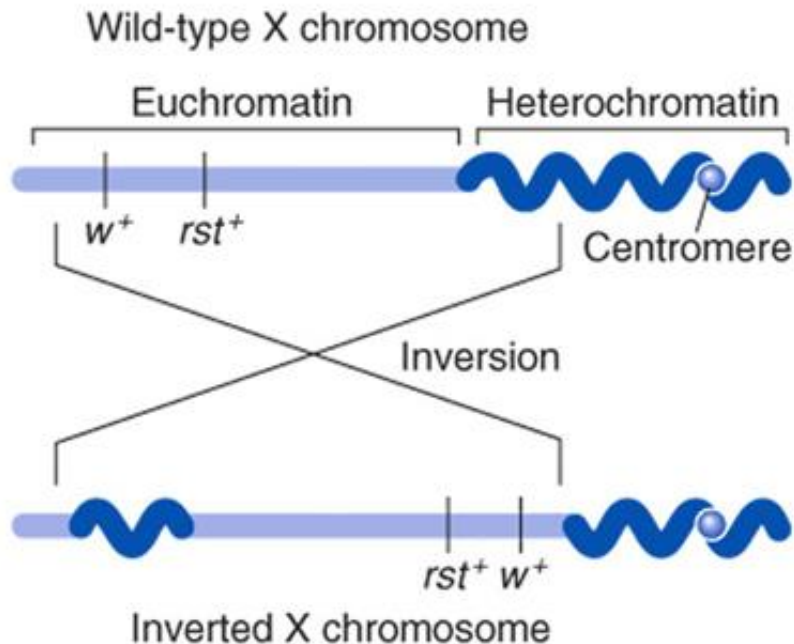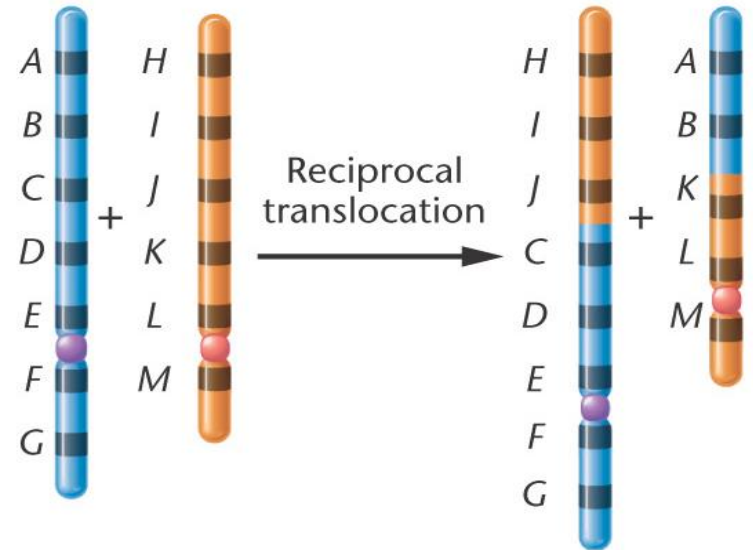
Reciprocal translocations

Symmetric

Asymmetric

Translocations: „nonreciprocal" and reciprocal

(d) **Nonreciprocal translocation of A–B**

(e) **Reciprocal translocation of A–B and H–I–J**
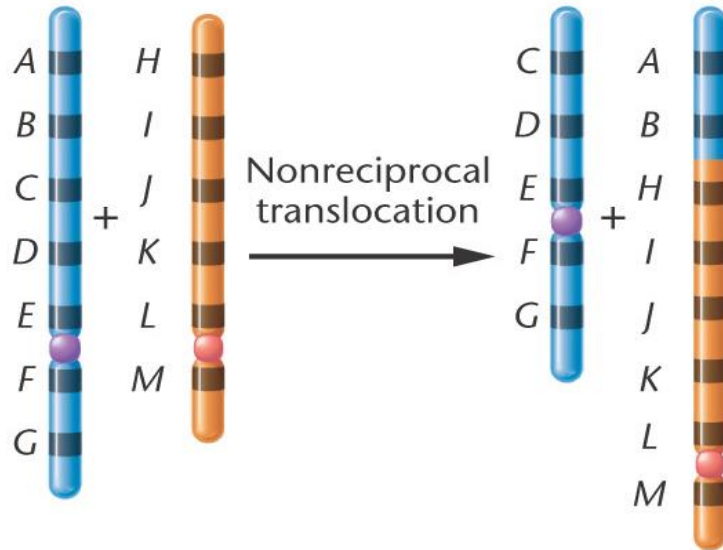
attachment of chromosome fragment to
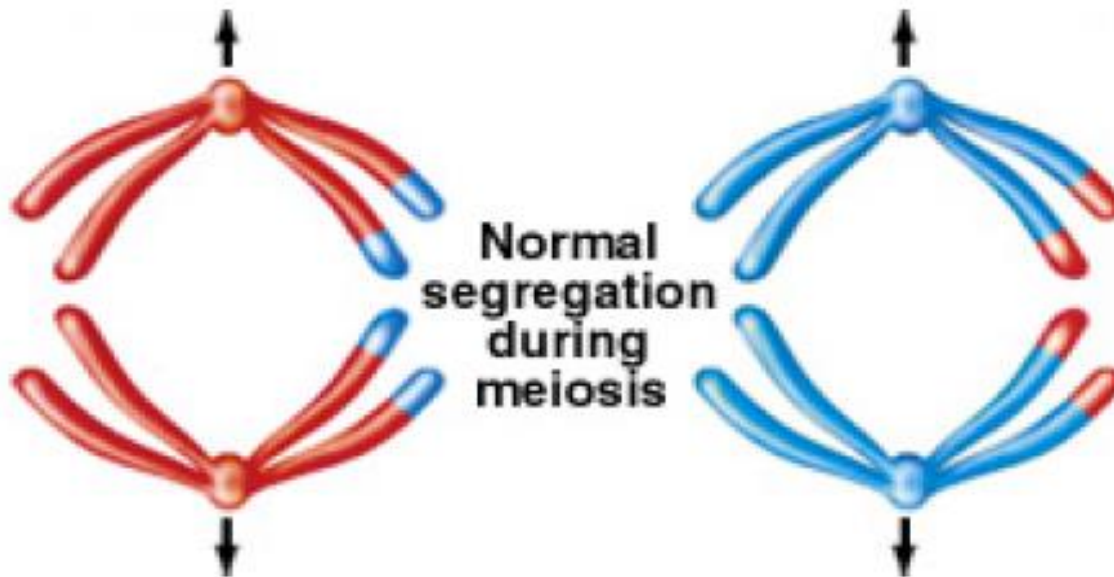a non-homologous chromosome (leading
to deletions and duplications in progeny)

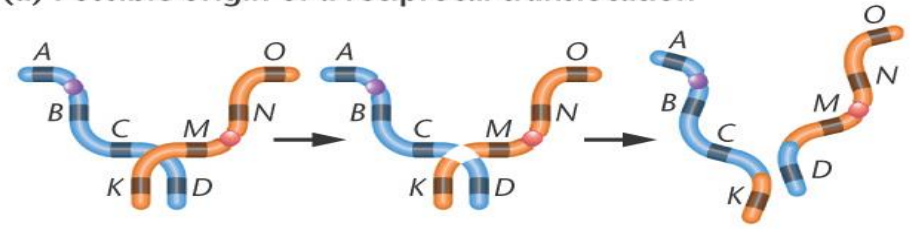exchange of chromosome fragments
between nonhomologous chromosomes

**Nonreciprocal translocations were not proven
experimentally! Infact all translocations are reciprocal.**

Reciprocal translocation: homozygotes
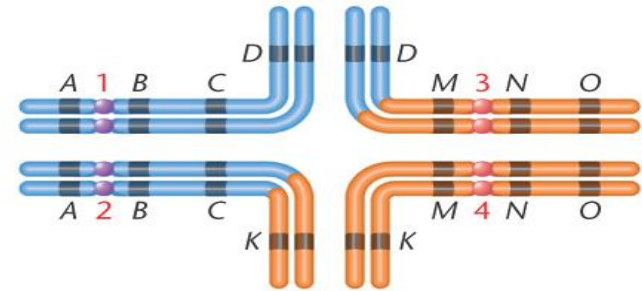

Normal segregation during meiosis
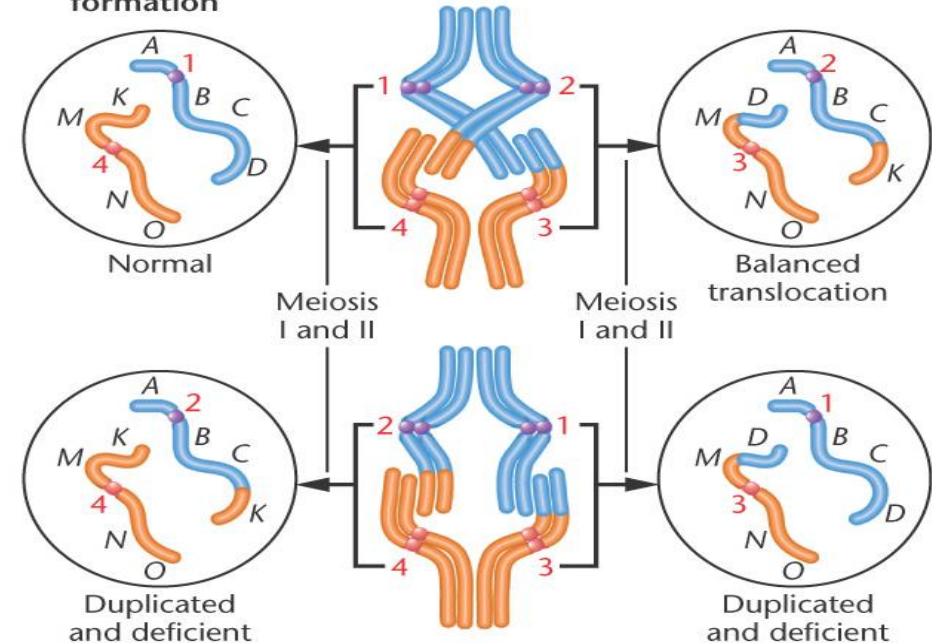
Reciprocal translocations: heterozygotes

(a) Possible origin of a reciprocal translocation

(b) Synapsis of translocation heterozygote

(c) Two possible segregation patterns leading to gamete formation

Normal

Meiosis I and II

Balanced translocation

Meiosis I and II

Duplicated and deficient

Duplicated and deficient

Two ways of segregation:

a) translocation chromosomes segregate together (balanced translocation)

b) translocation chromosomes are separated > > gametes with duplications and deletions (imabalanced gametes) > > 50% of the gametes are not viable (= semisterility)

Robertsonian translocations – ROBs (centric „fusions")

- type of a reciprocal translocation between two acrocentric chromosomes

- also called whole-arm translocations or centric-fusion translocations

- named after the American insect geneticist W. R. B. Robertson, who first described a Robertsonian translocation in grasshoppers in 1916

- evolutionary significance >>> **chromosome number reduction** (from 2 acrocentric chromosomes one metacentric chromosome)

Dicentric ROB
(more frequent)

Monocentric ROB

lost

lost
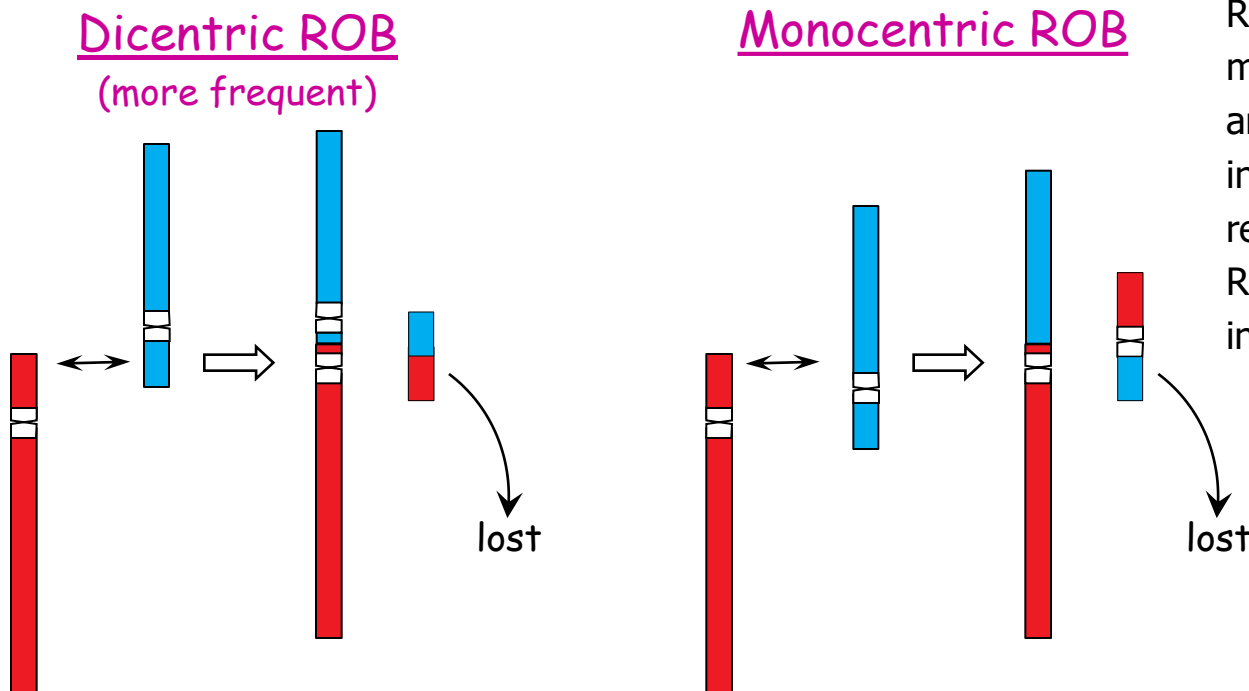
Robertsonian translocations are the most common recurrent structural anomaly in humans, with about 1 in 1000 individuals carrying this rearrangement. The carriers of ROBs have 45 chromosomes instead of the normal 46.

Familial or translocation Down syndrome:
Robertsonian translocation and its consequences

„fusions" of long arms of two acrocentric chromosomes (13, **14**, 15, **21** and 22)
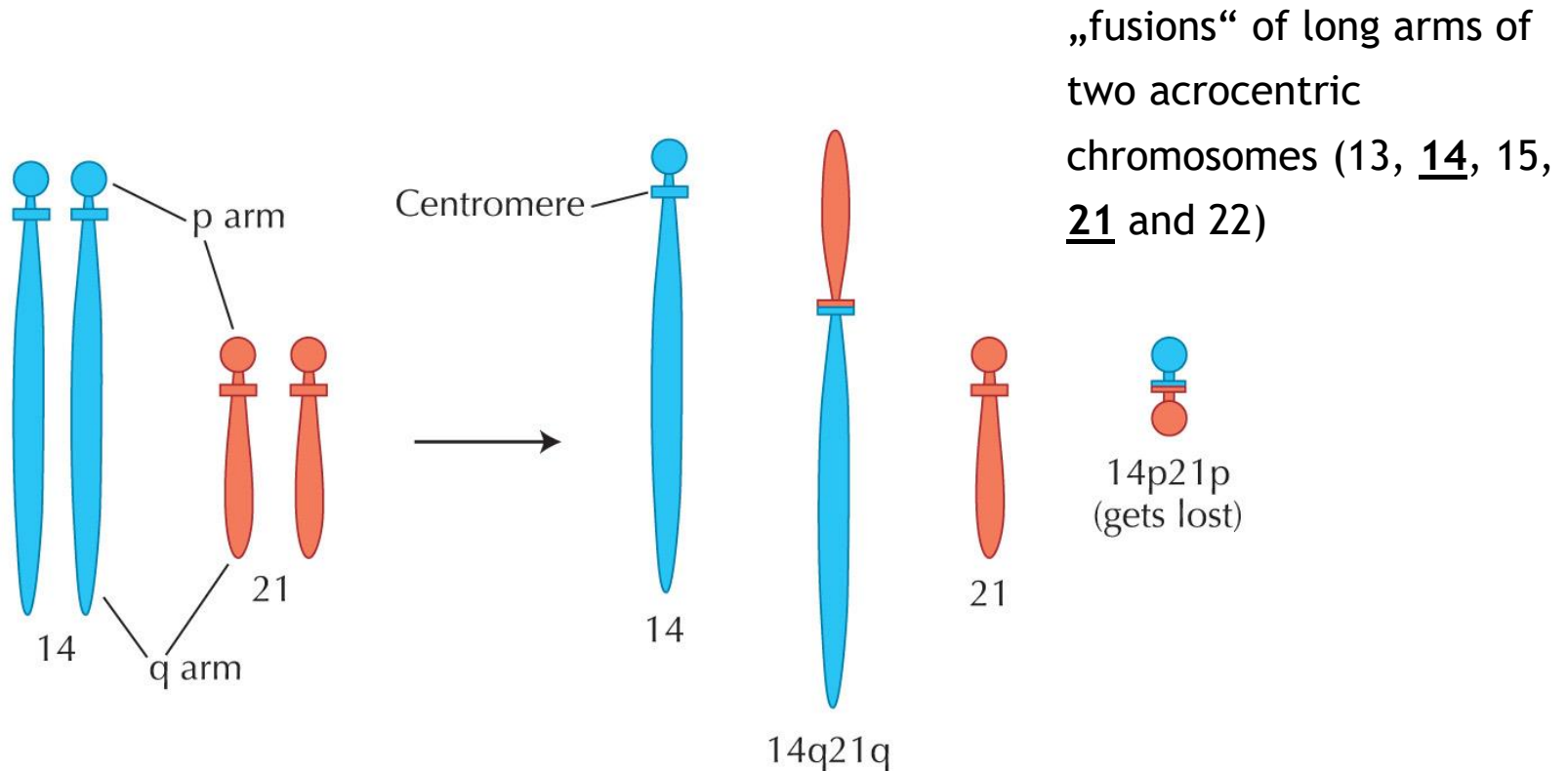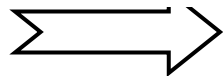

FIGURE 12.6. Translocation. Diagram of translocation between human chromosomes 14 and 21. The short (p) arms of chromosomes 14 and 21 can recombine, causing the two translocations (14q21q and 14p21p).

Familial Down syndrome

- Most of long arm from chromosome 21 translocated to 14 (14/21 translocation)

- „Fusion" occurs at two rDNA regions on the chromosomes
  - about 20% rDNA copies lost
  - carrier still normal (2n = 45)
  - woman is usually a carrier of the 14/21 chromosome