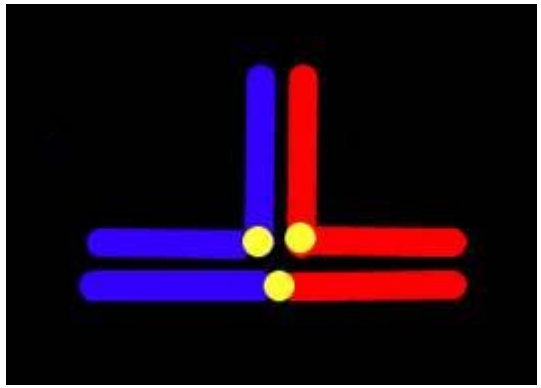
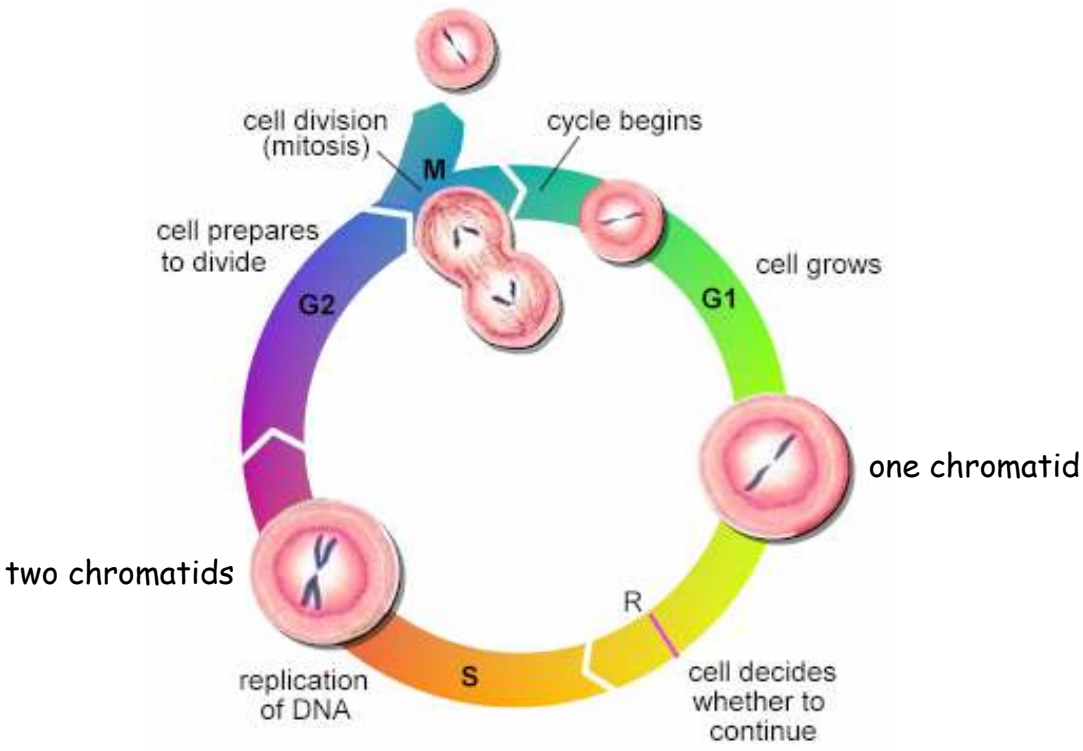
Chromosomal mutations

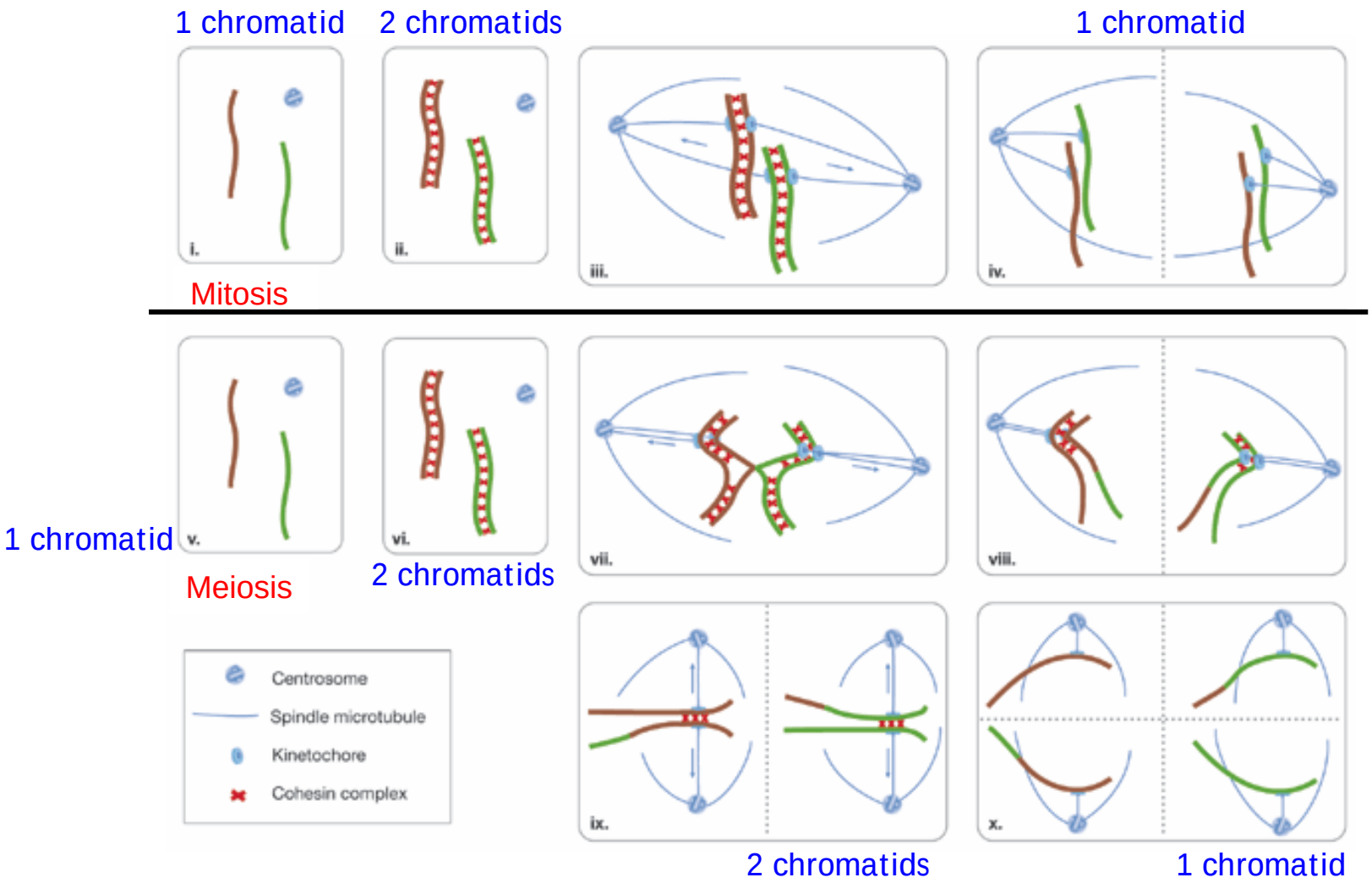
(chromosome rearrangements)



Chromosomes throughout cell cycle



Chromosomes and chromatids during mitosis and meiosis



Chromosome mutations

are variations in:

1. Chromosome structure (chromosomal rearrangements)
   - deletions
   - duplications
   - translocations
   - inversions
   - transpositions
2. Chromosome number
   - aneuploidy
   - abnormal euploidy

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 chromosome segment 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

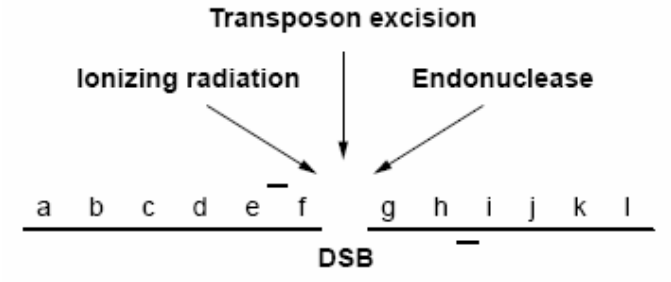
- if the two ends of the same break are rejoined >> the original DNA order restored, **if ends of two different breaks are joined together (= mis-repair of DNA demage) >> chromosomal rearrangement**

- 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

How double-strand breaks are generated

DSBs are caused by several factors:

- arrest of replication and restart of DNA synthesis (replication forks tend to stall in regions of repeat elements - e.g. tRNA genes, retroposons, and telomeres); major source of DSBs!

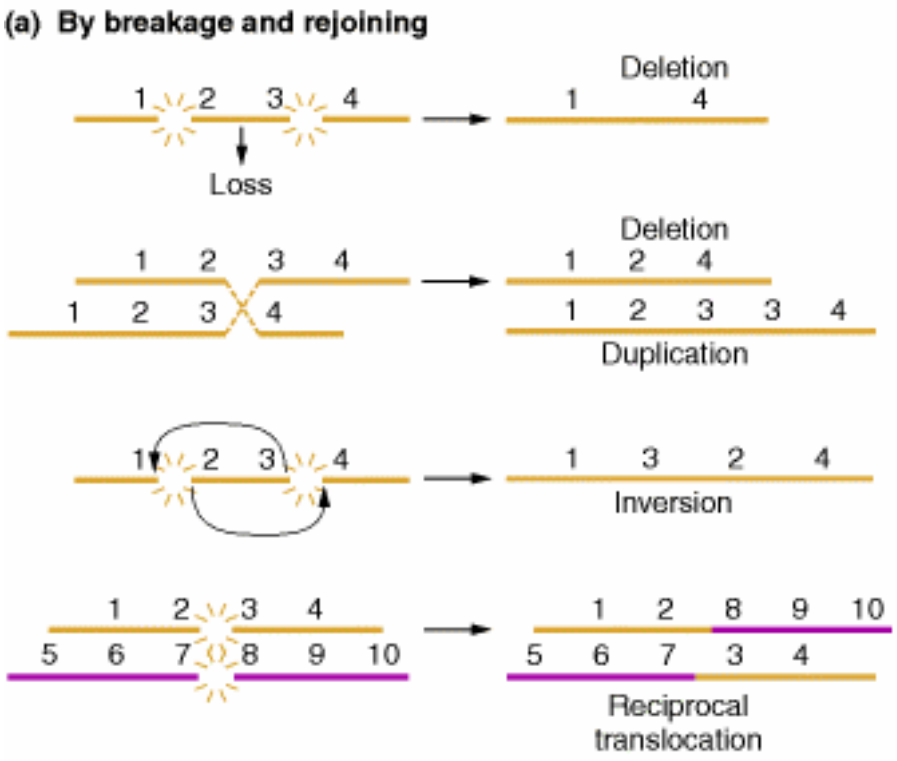


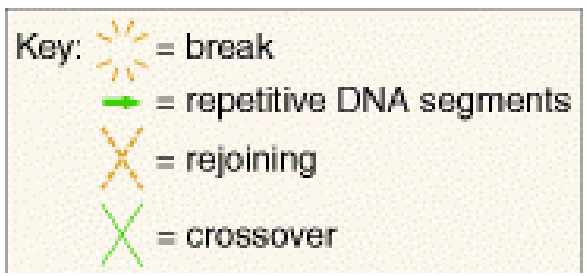
- during meiotic recombination
- mechanical pulling (e.g. in dicentric chromosomes)
- experimentally (radiation by X-rays, DNA transposons, rare cutting restriction endonucleases)

.....

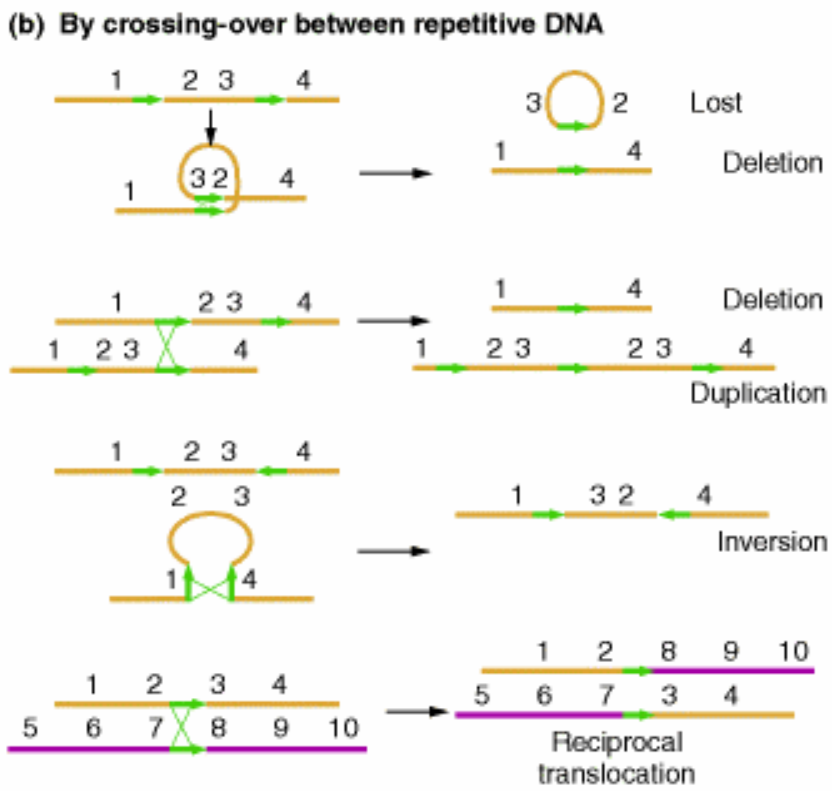
- ❖ in vegetative (mitosis) and generative cells (meiosis)
- ❖ DSBs have to be repaired before genomes are replicated (S phase)
- ❖ in plants, errors in DSB repair (DSBs misrepair) can have the evolutionary significance because changes in meristematic cells can be transferred to the offspring >>> chromosome rearrangements

Origins of chromosome rearrangements





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.



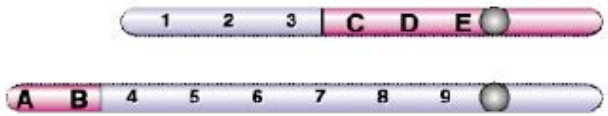
Chromosome rearrangements

Deletions

Duplications

Inversions

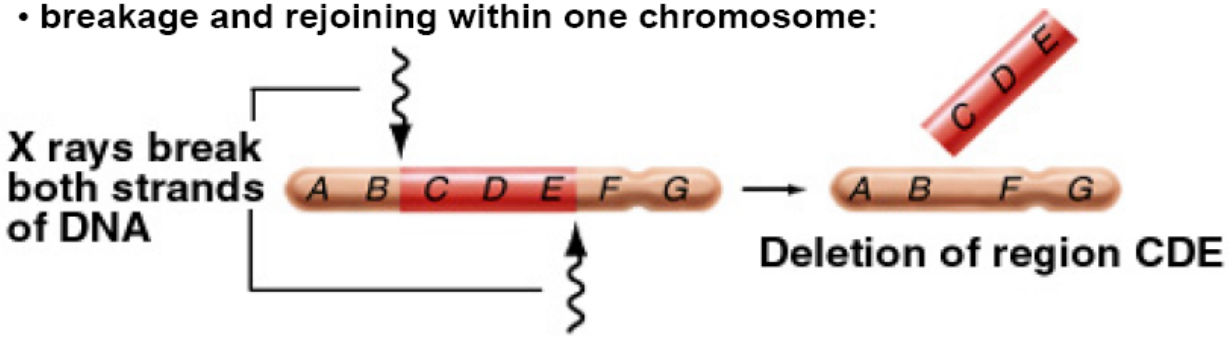
Translocations

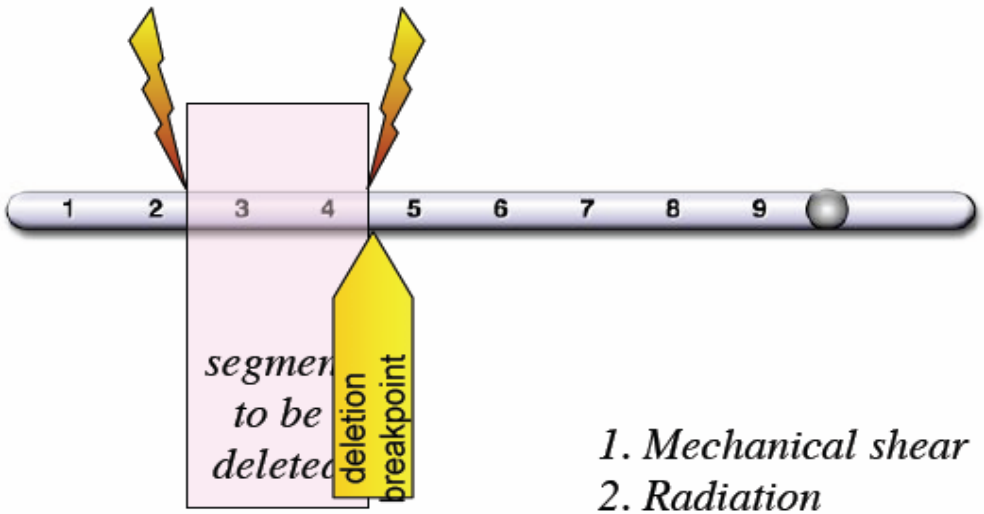


Deletion formation by breakage and rejoining

= deficiencies = losses of chromosome segments

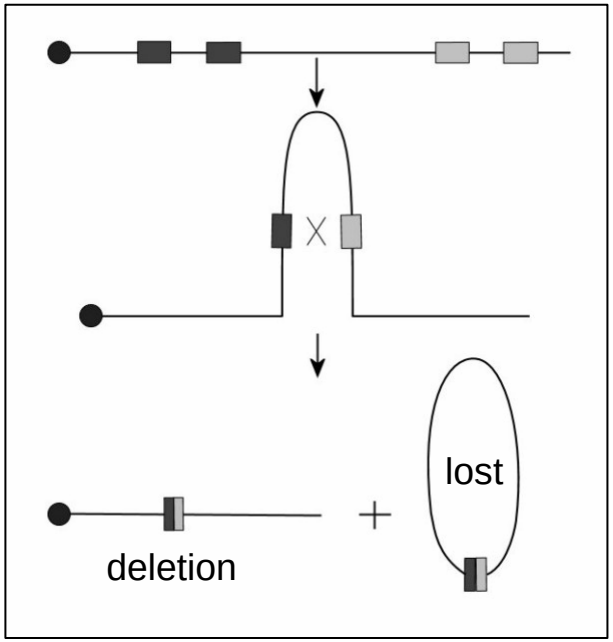
- can occur terminally or internally, e. g. caused by…
  - breakage and rejoining within one chromosome:



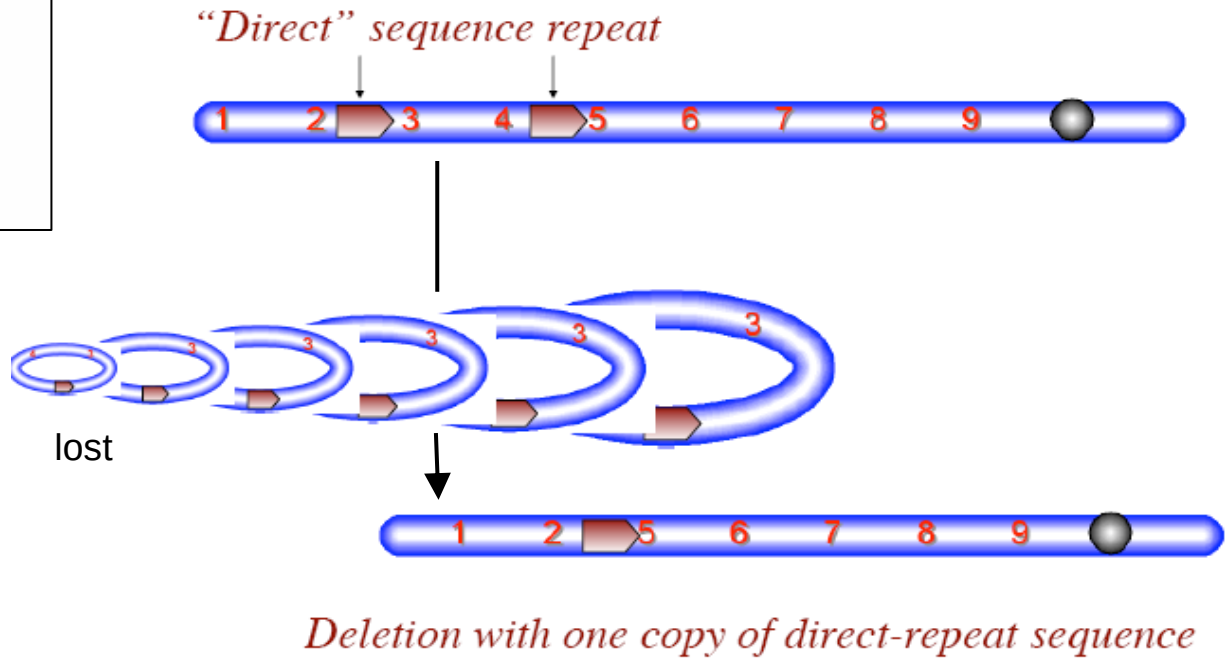


1. *Mechanical shear*
2. *Radiation*
3. *Transposable elements*

Deletion formation by intra-chromosomal crossover



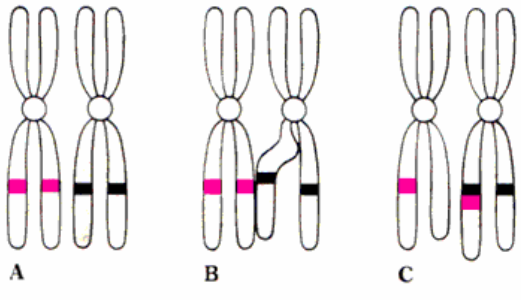
another example…

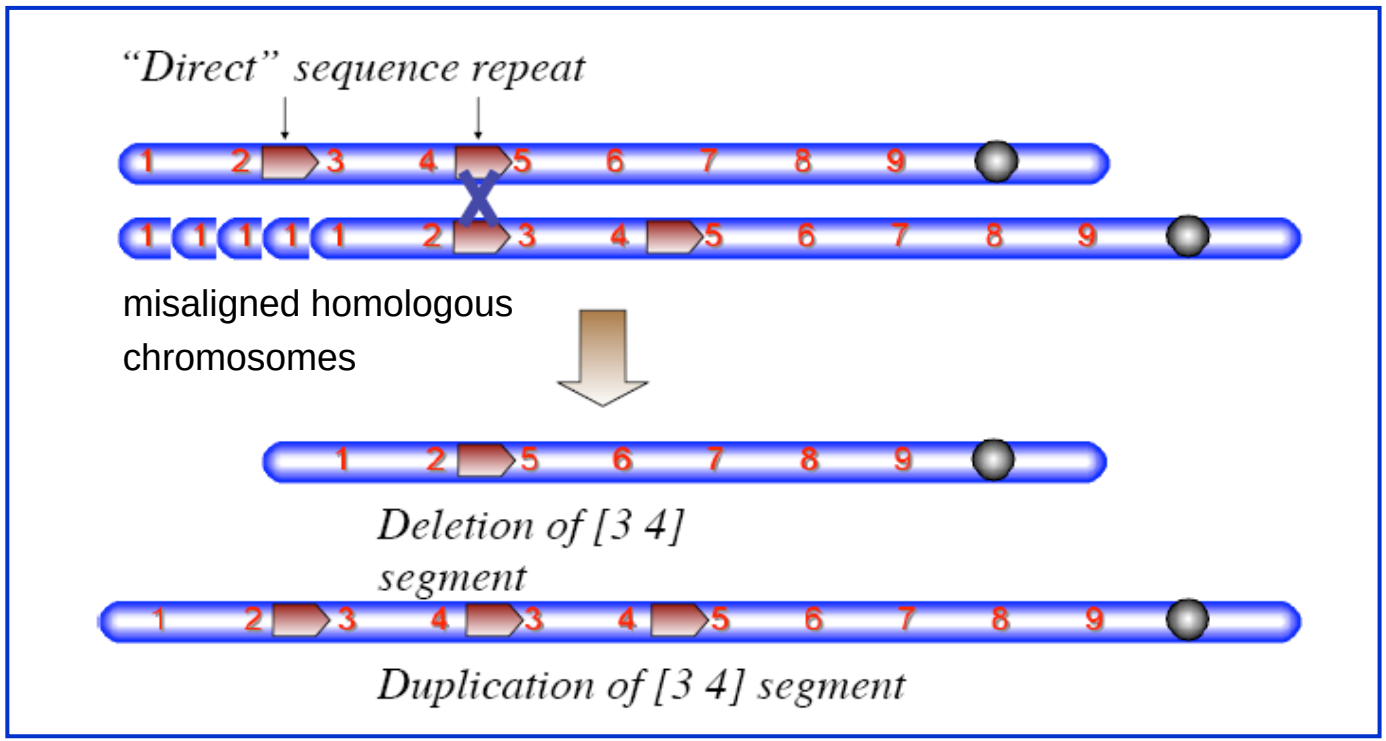


Deletion with one copy of direct-repeat sequence

Deletion (and duplication) formation by unequal cross-over

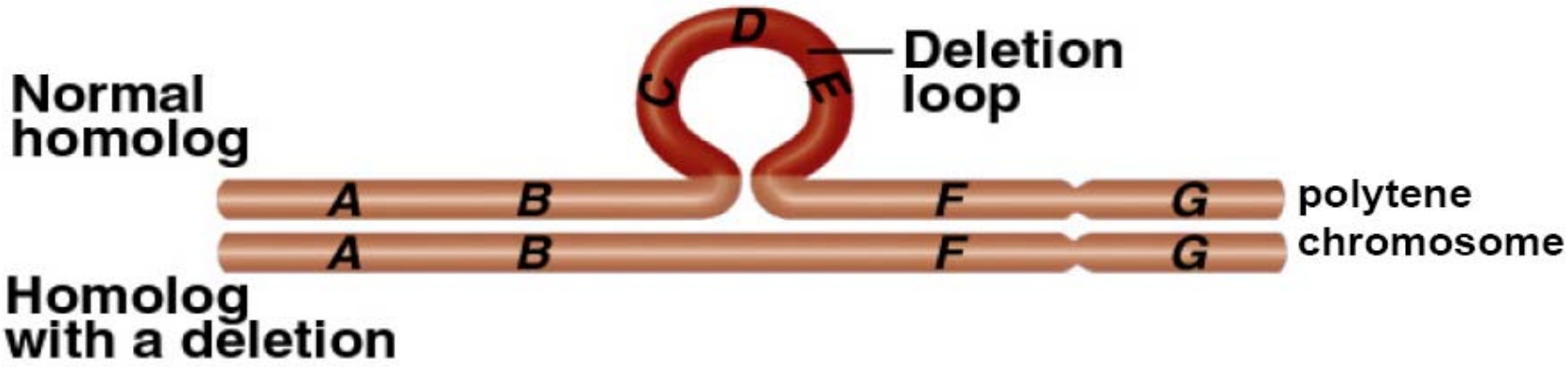
Sometimes during meiosis two chromatids from homologous chromosomes **(A)** are misaligned during a cross-over event **(B)** as a result, one chromatid gained a duplicated region and the another lost a deleted region **(C)**. The duplication as well as the deletion are inherited by resulting gametes.





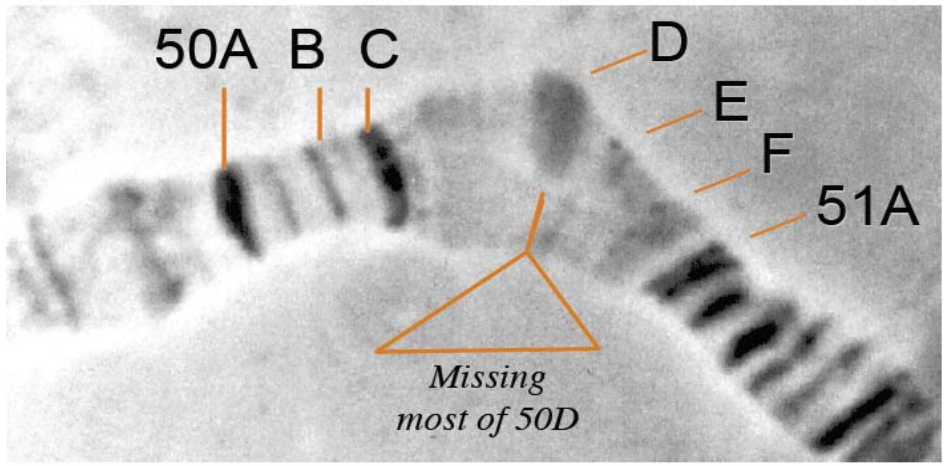
How deletions can be identified

by finding a visible change in chromosome structure:

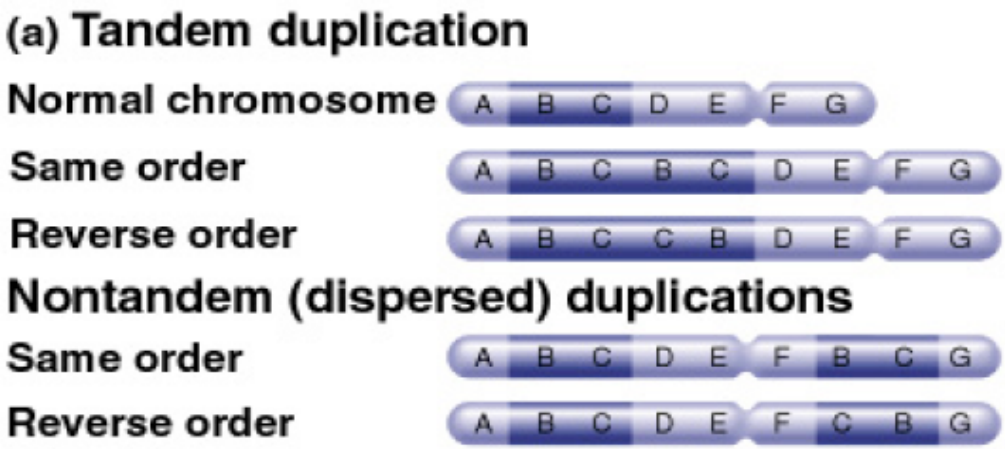


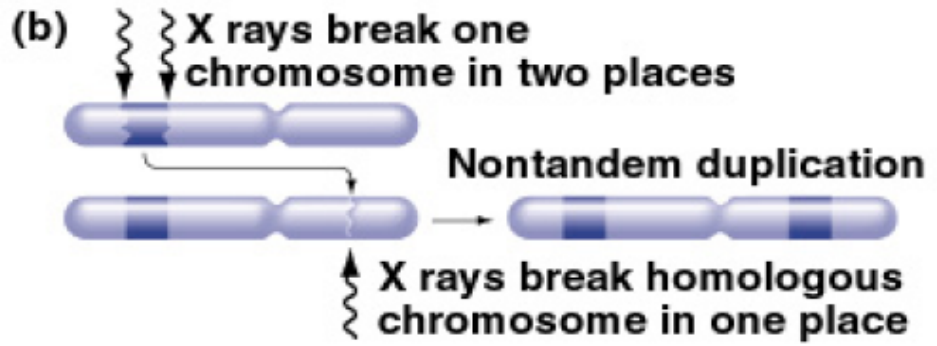
polytene chromosomes

Drosophila deletion heterozygote



Duplications

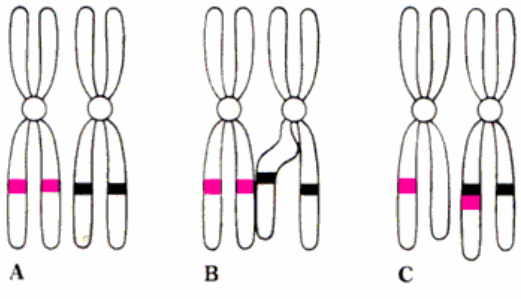


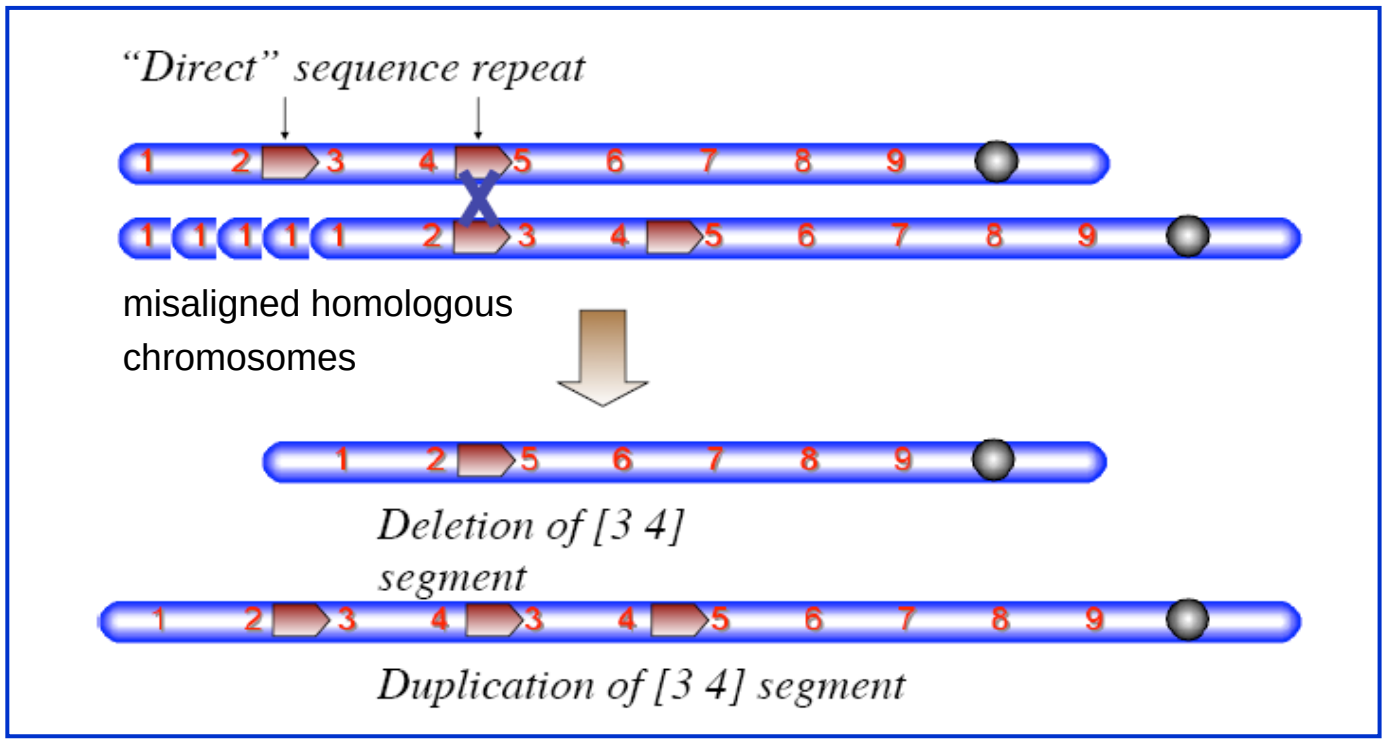


Duplication (and deletion) formation by unequal cross-over

- 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.





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"

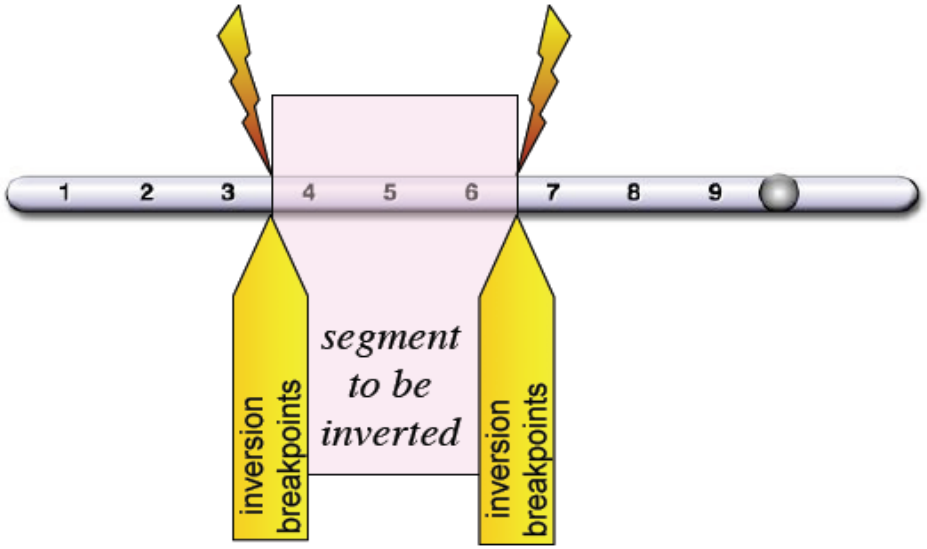
Gene duplication produces a reservoir of genes from which to evolve new ones. Why reinvent the wheel from scratch?

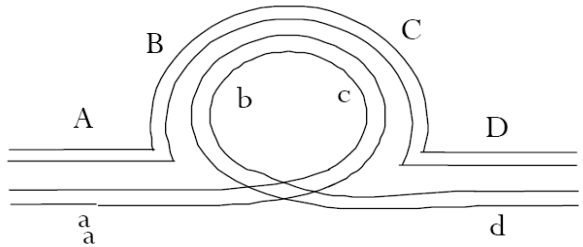
- evolution of RNA genes
- in particular rRNA genes (rDNA)
- 5-10 copies/bacterial genome
- c. 130 copies/Drosophila genome
- *Xenopus* c. 400 copies/genome (but the oocyte may have 1500 micronuclei, each with a NOR, it is c. 600,000 copies of rDNA)

Inversions

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

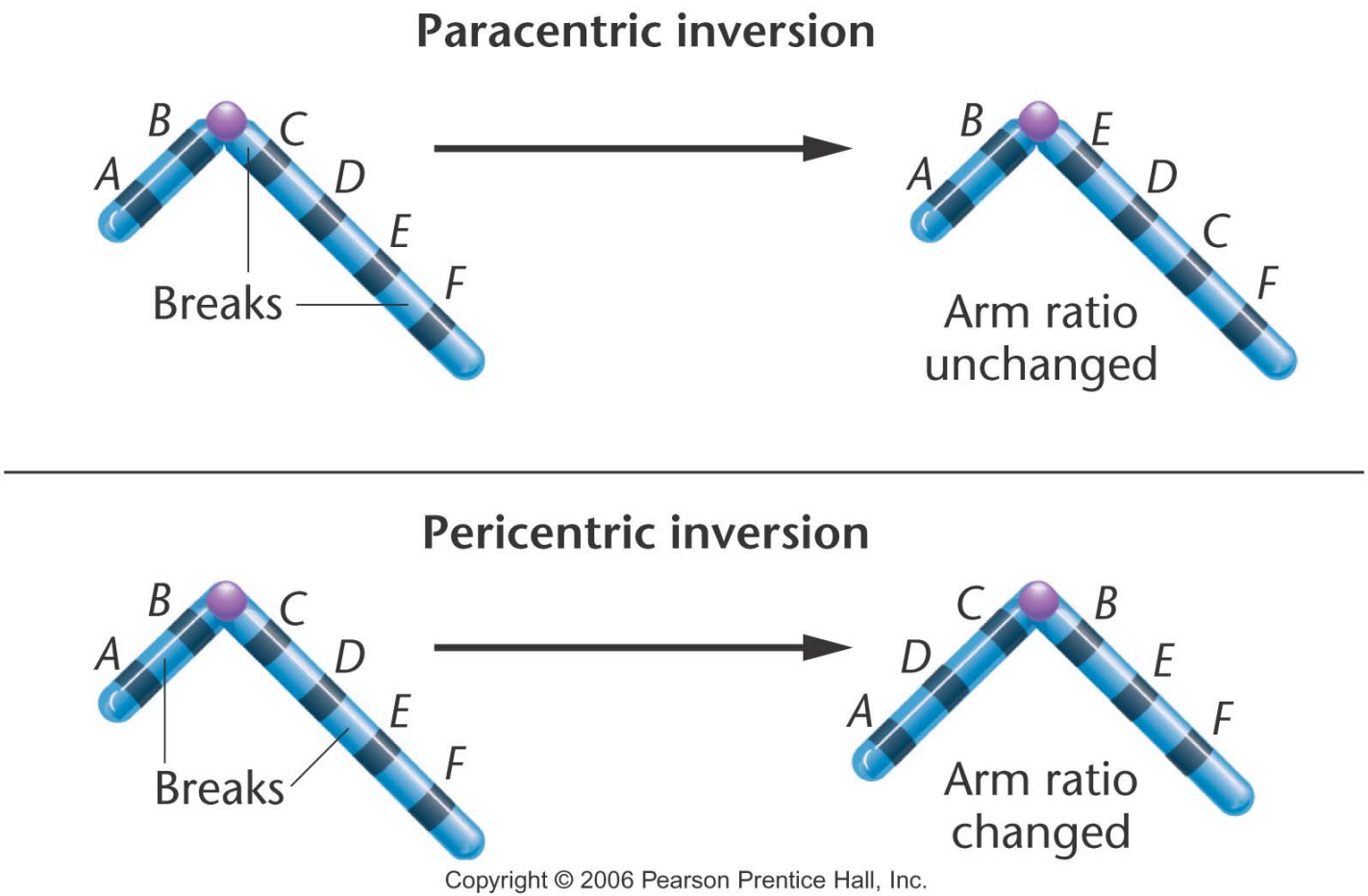
Inversion heterozygote - cells that contain one normal haploid chromosome set plus one set carrying the inversion. Microscopic observation of meioses in inversion heterozygotes reveals an **inversion loop**.





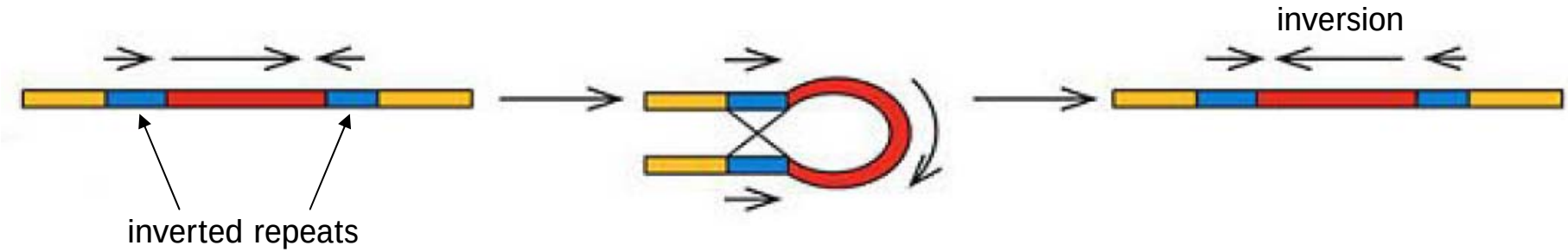
meiotic inversion loop

Two types of inversions



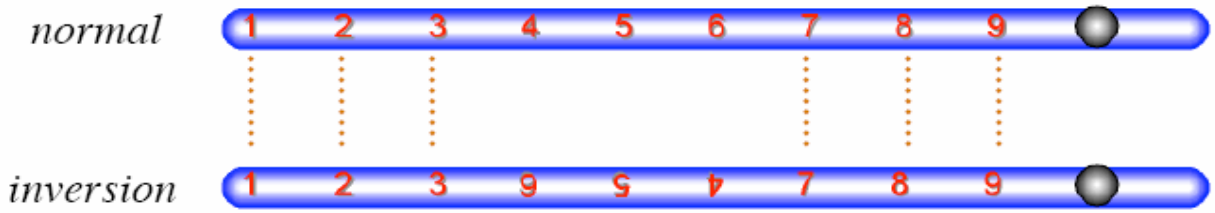
mechanism of inversion formation: breakage and rejoining

Inversion formation by intra-chromosomal crossover

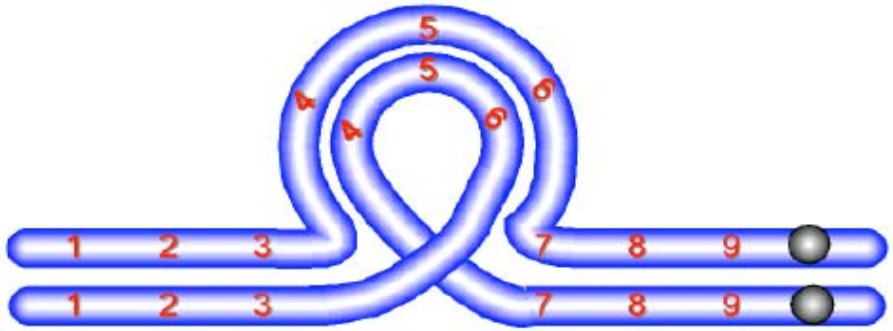


How the chromosomes pair in an inversion heterozygote?

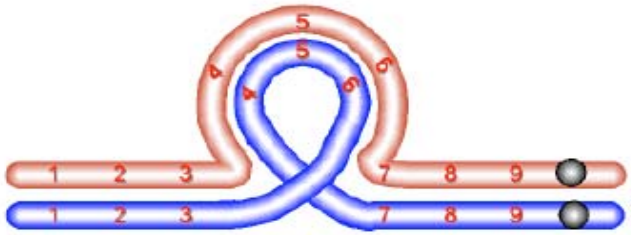
(paracentric) inversion heterozygote



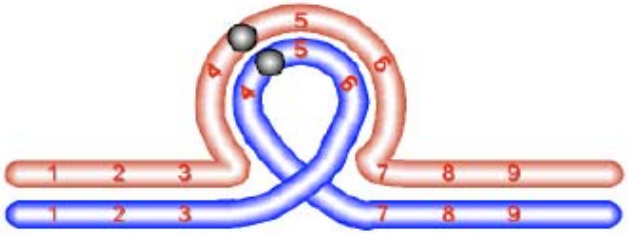
by forming an inversion loop…



Inversion loops in para- and pericentric inversion heterozygotes



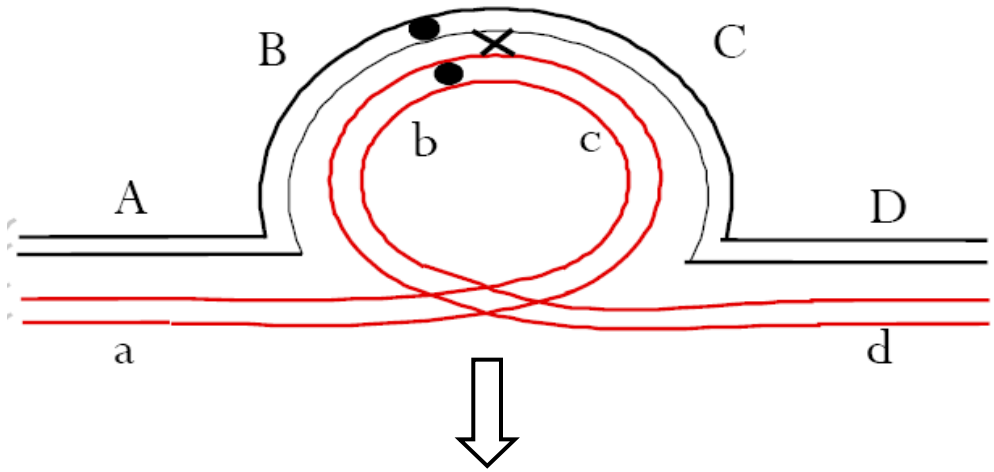
paracentric inversion



pericentric inversion

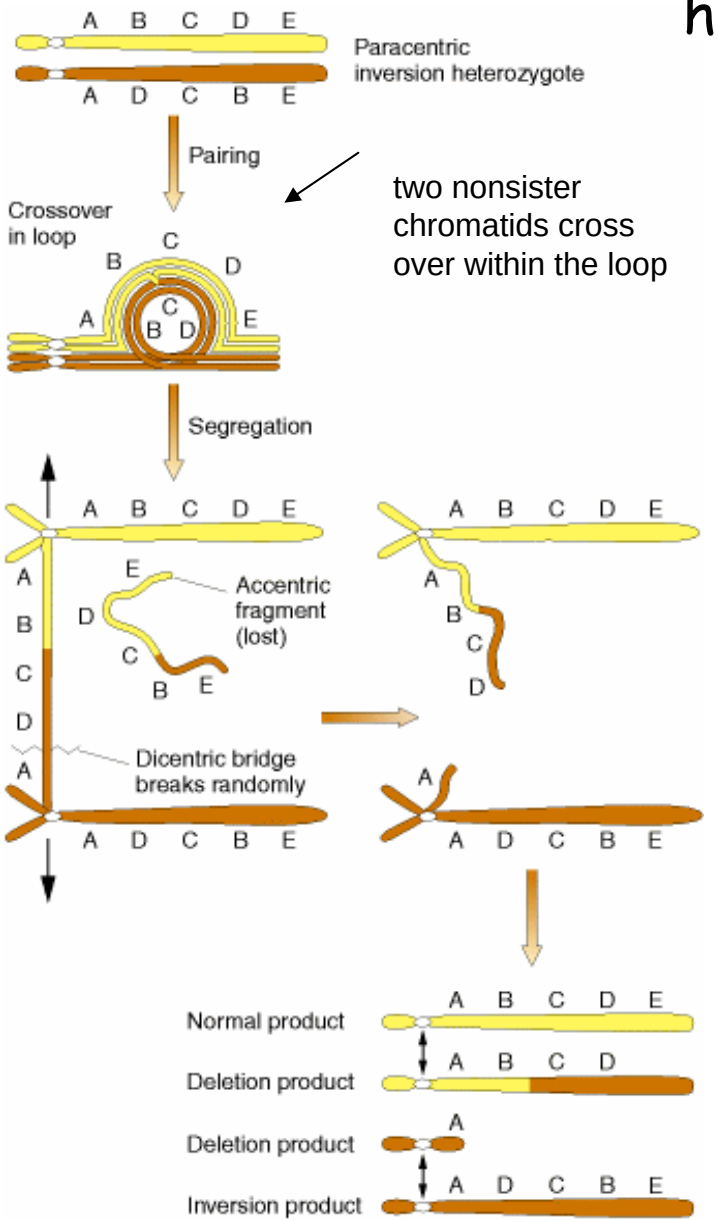
When no recombination occurs, 50% of gametes have inversion. Next two slides show what happen if a recombination event does occur in the inversion loop…

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



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

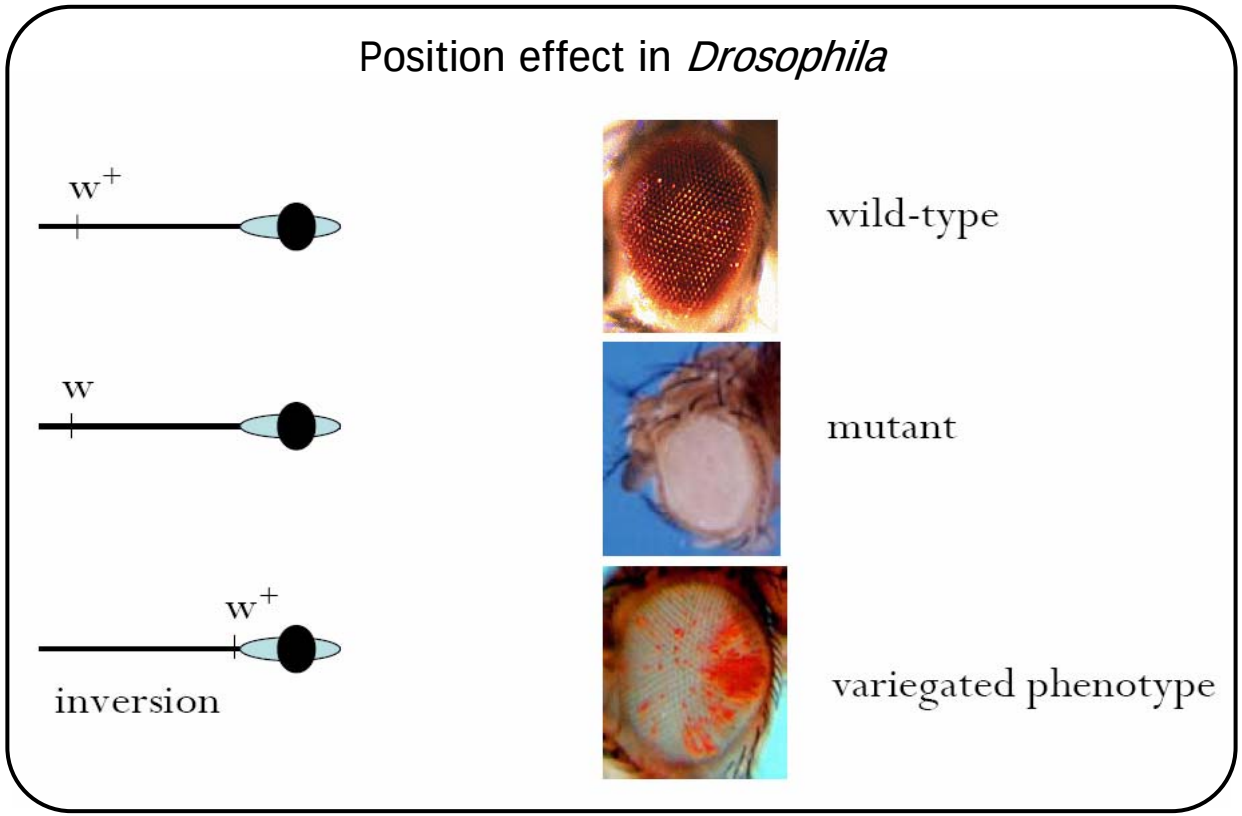
Anaphase I

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

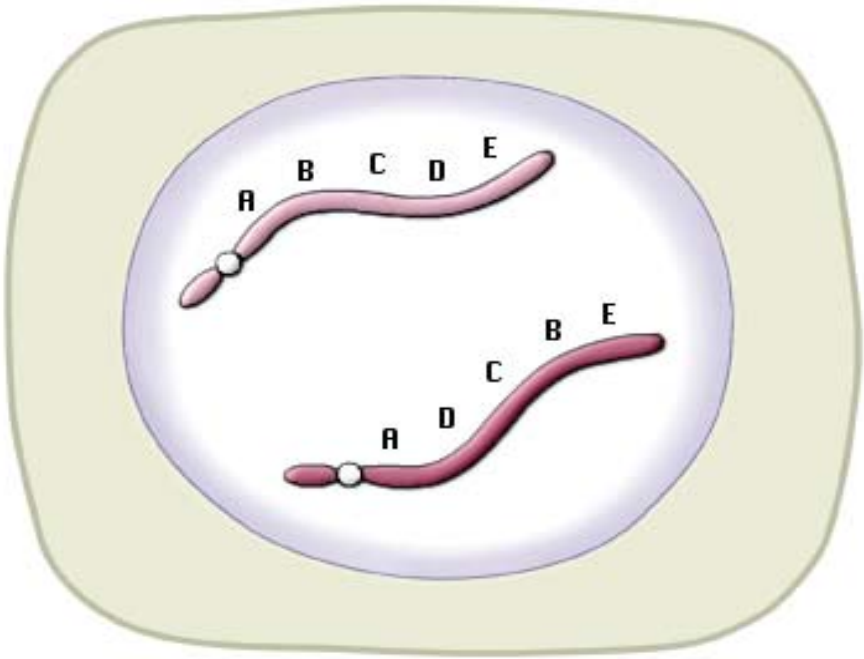
Gametes containing deleted chromosomes may be inviable, but, even if viable, the zygotes that they eventually form will probably be inviable. Crossing-over generates here lethal products. The overall result is a lower recombinant frequency. Inversions affect recombination in another way, too. Inversion 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)*

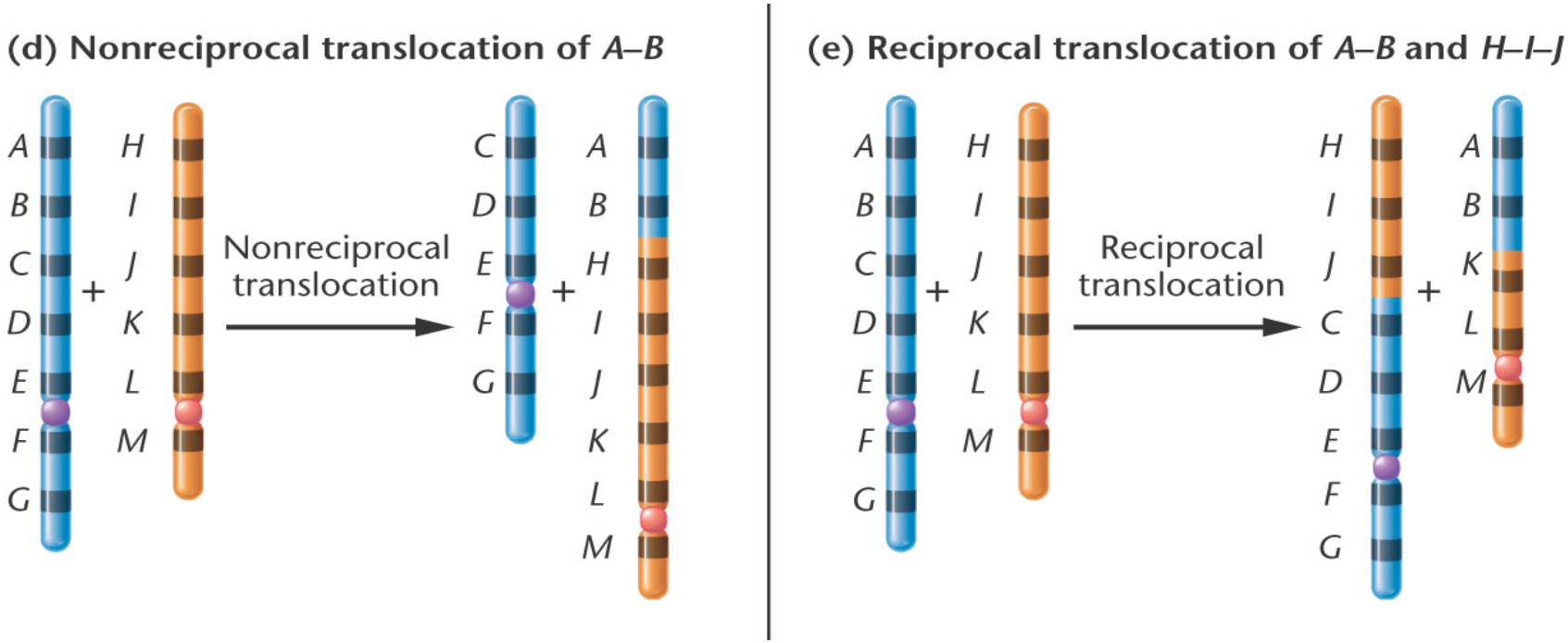


Inversions are crossover suppresors – evolutionary consequences



(more information on the role of inversions in speciations in next lecture)

Translocations: nonreciprocal and reciprocal



attachment of chromosome fragment to a non-homologous chromosome (leading to deletions and duplications in progeny)

exchange of chromosome fragments between non-homologous chromosomes

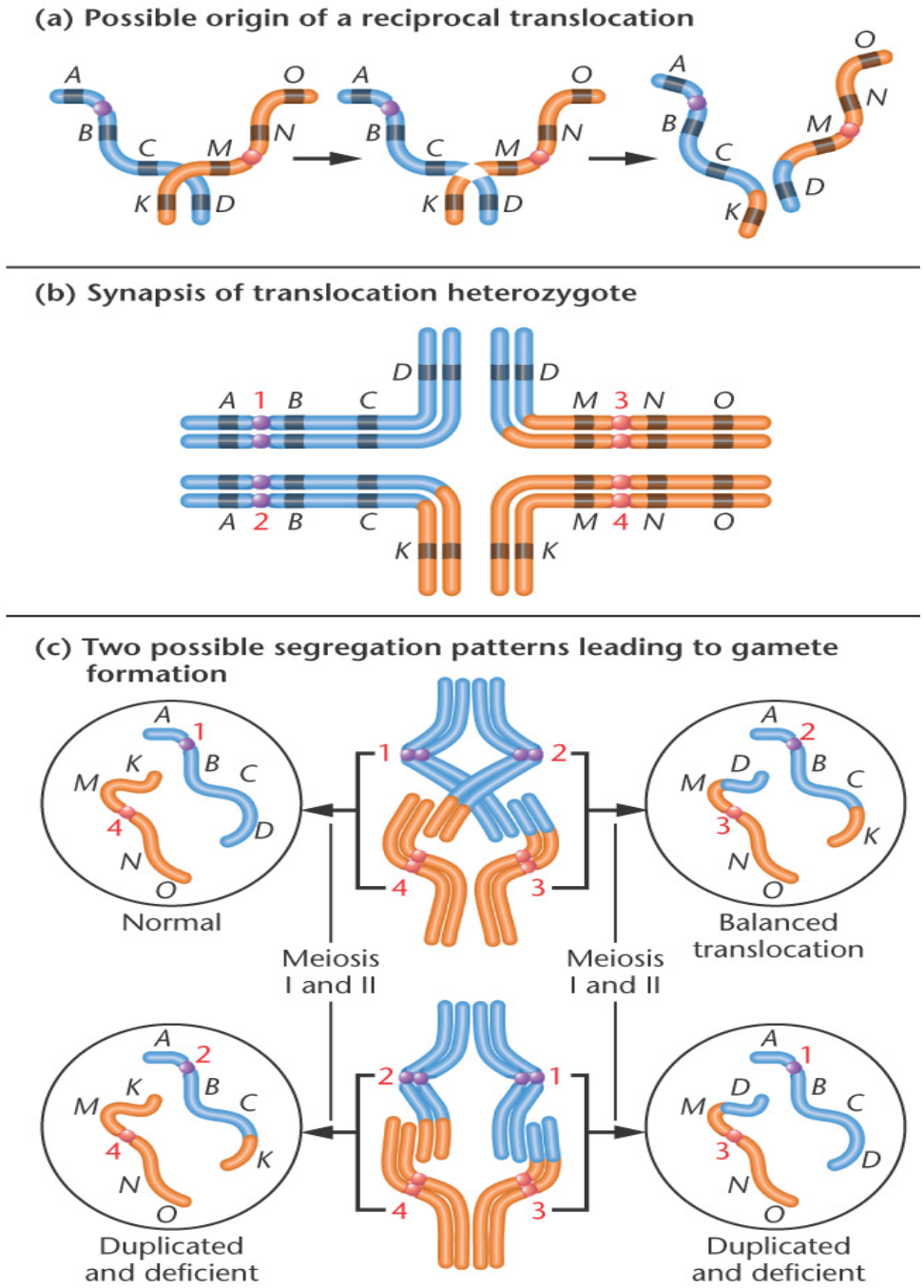
Reciprocal translocations

Reciprocal translocations result from crossover events between non-homologous chromosomes

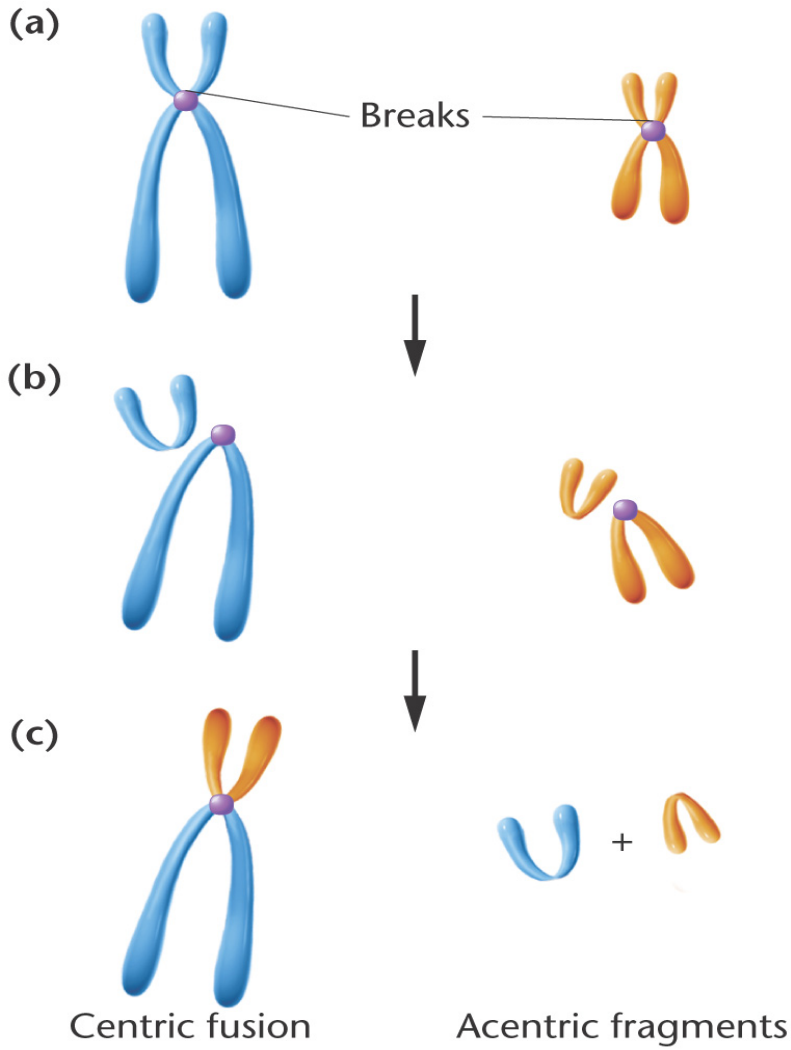
Two ways of segregation:

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)



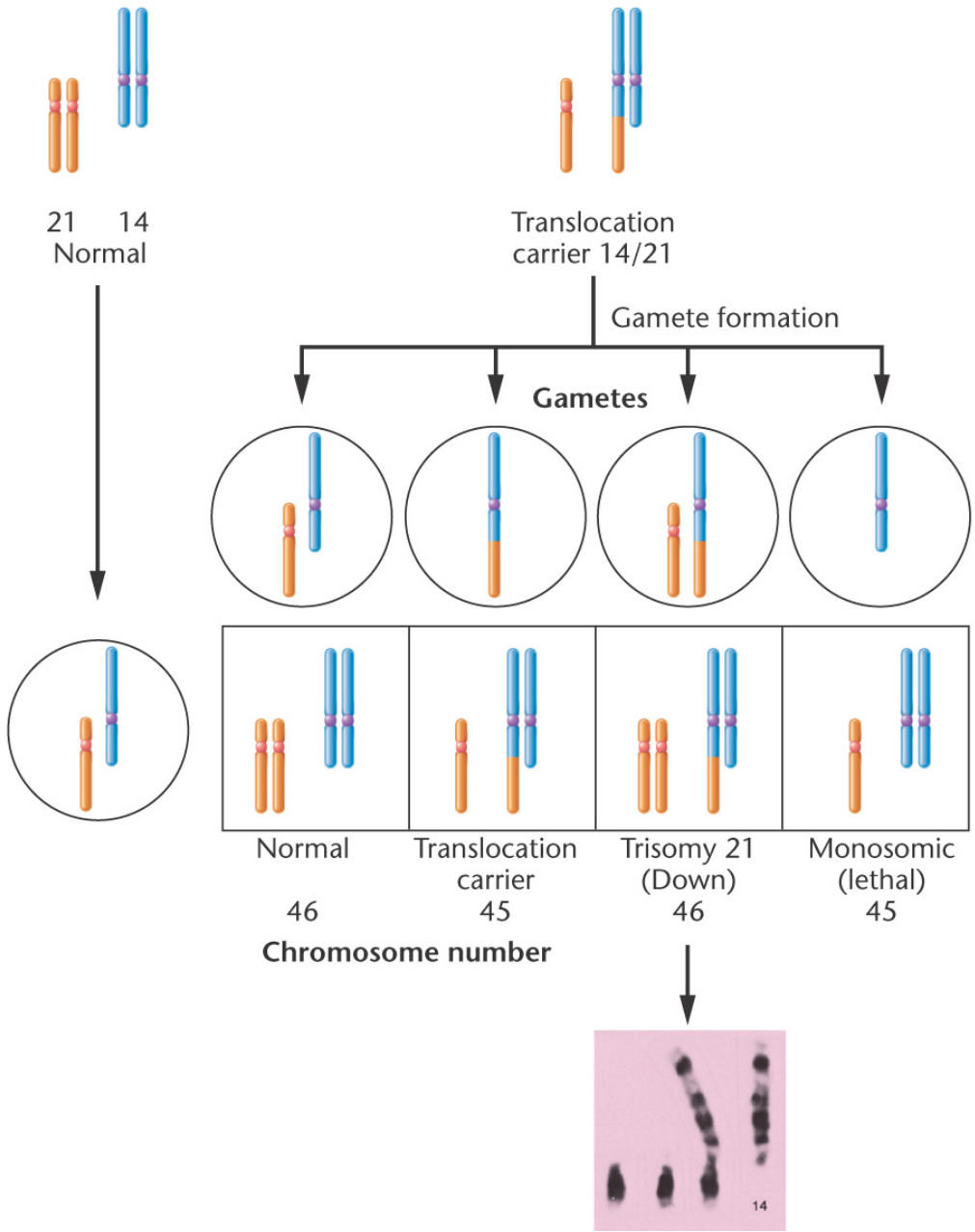
Nonreciprocal translocation and its consequences (familial Down syndrome)



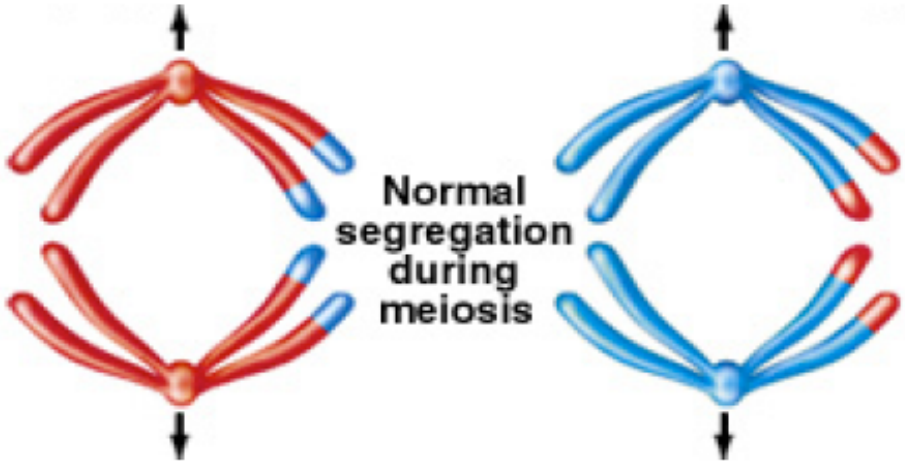
fusions of long arms of two acrocentric chromosomes (13, **14**, 15, **21** and 22)

Nonreciprocal translocation and its consequences (familial Down syndrome)

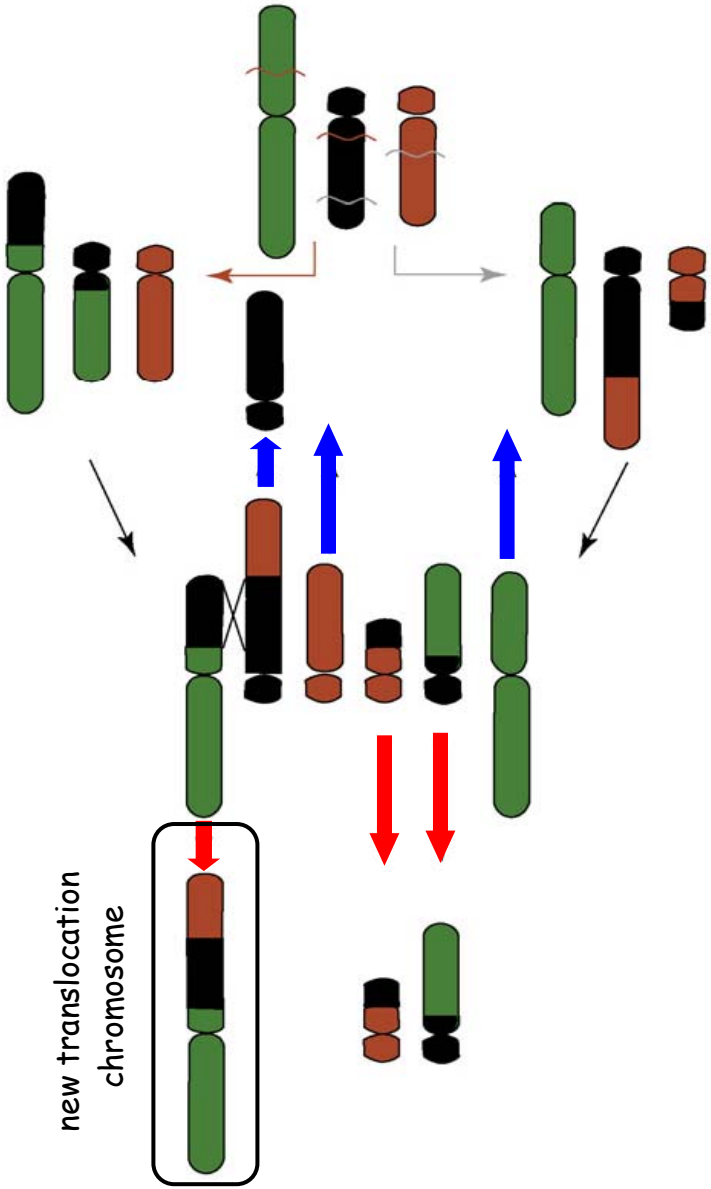
- Most of long arm from chromosome 21 translocated to 14 (14/21 translocation)
- Fusion occurs at two rDNA regions on the chromosomes
  - about 20% rDNA copies lost
  - carrier still normal
  - trisomy 21 (Down)



Reciprocal translocation: homozygotes



Secondary reciprocal translocation



normal (“wildtype”) karyotype (n=3)

↓

2 types of translocation heterozygotes

↓

crossing

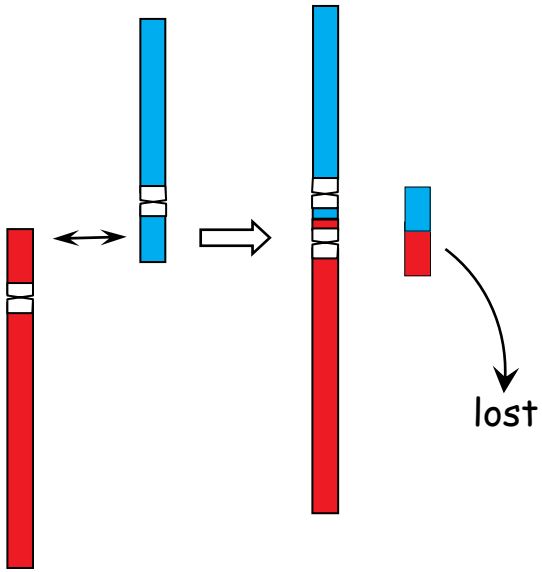
↓

meiosis: crossover (X) between partially homologous chromosomes
- the new chromosome segregates together with the other two translocation chromosomes to one pole (arrows down), on the other pole the wildtype karyotype is reconstituted (arrows up)

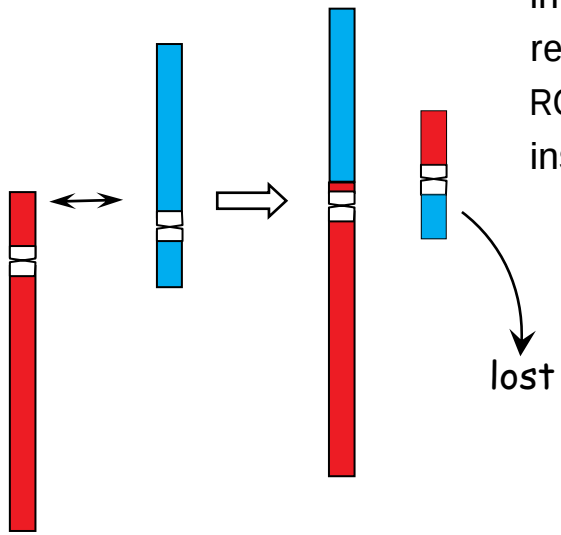
Robertsonian translocations - ROBs (centric fusions)

- 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)



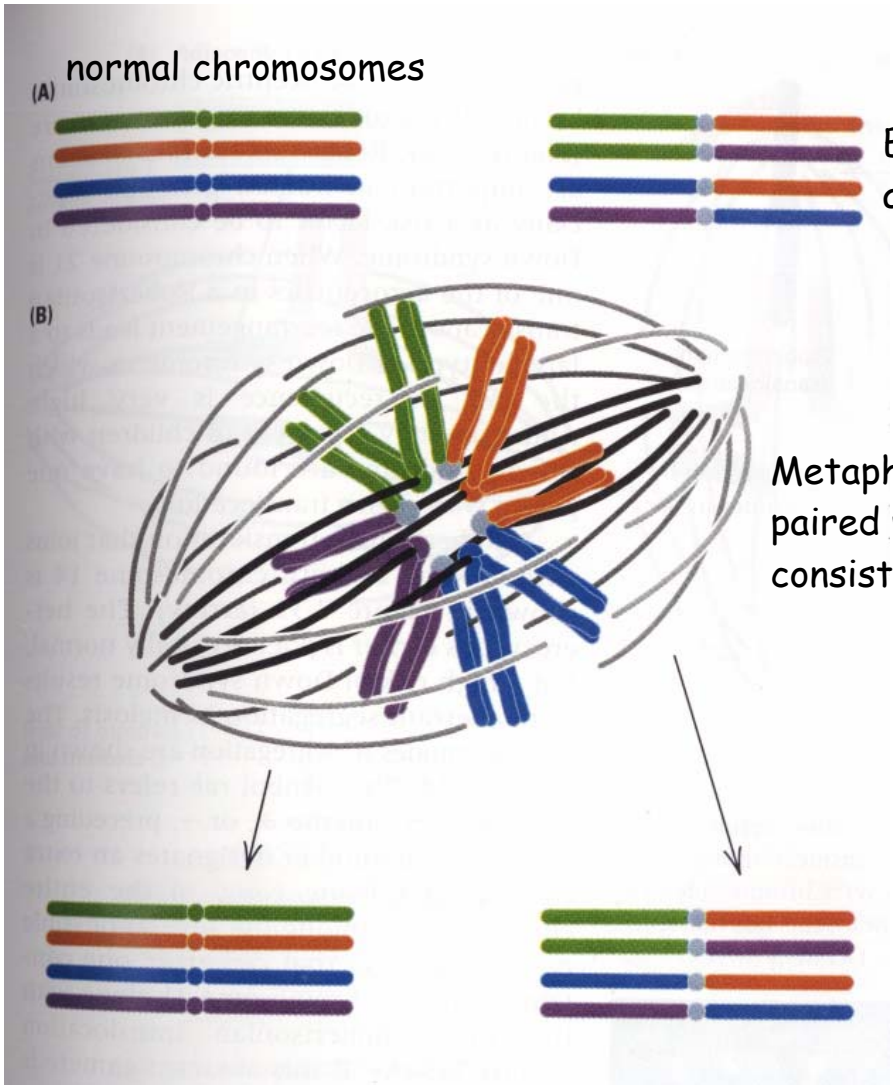
Monocentric ROB



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.

Permanent translocation heterozygotes

Translocation heterozygotes segregate the chromatides from the tetrades in such a way that there are two kind of gametes (a non-translocated set of chromosomes and a translocated set of chromosomes). Example: evening primrose (*Oenanthera*).



Each chromosoma have exchanged an arm with the next chromosome

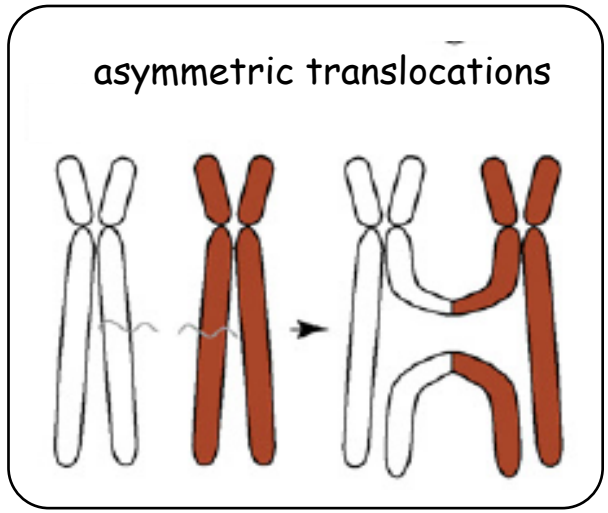
Metaphase I: a ring of chromosomes, each arm is paired with its proper partner (each chromosome consists of two chromatids)

Alternate segregation yields two types of gametes: gametes with all normal chromosomes, and gametes with all translocated chromosomes

Breakage-fusion-bridge cycle (BFB cycle)

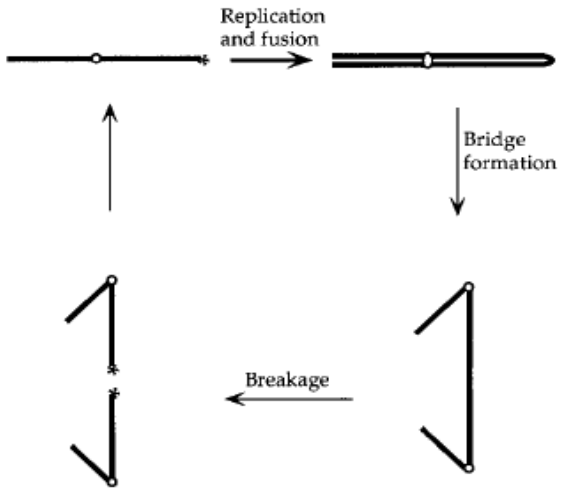
- described by B. McClintock (1940) in maize (*Zea mays*)
- chromosomes are broken by various means (asymetric translocation)
- the adhesive broken ends fuse with one another
- a chromatid bridge is produced as the two centromeres of the terminally united chromosomes pass to opposite poles in this mitotic anaphase
- the tension on the anaphase bridge due to the poleward migration of the centromeres, results in breakage
- chromatids with broken ends enter sister telophase nuclei
- the cycle can be stopped by addition of telomeric sequences at the breakpoints
- in maize, BFB cycle only in endosperm, not in zygote (broken ends healed by telomeric sequences)

Barbara McClintock

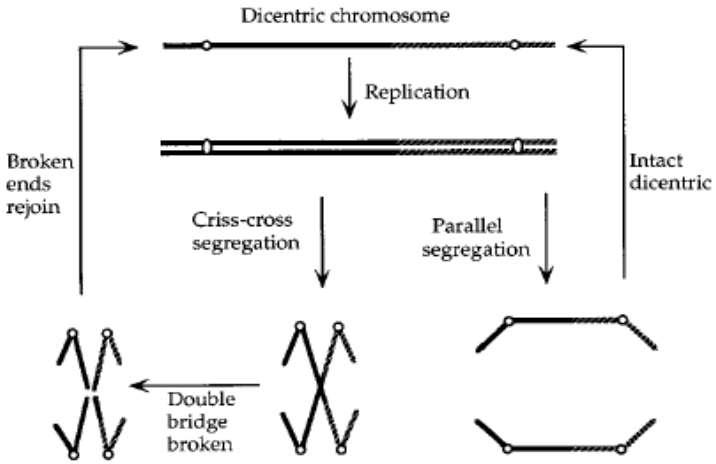


Breakage-fusion-bridge cycles (BFB cycles)

chromatide type



chromosome type



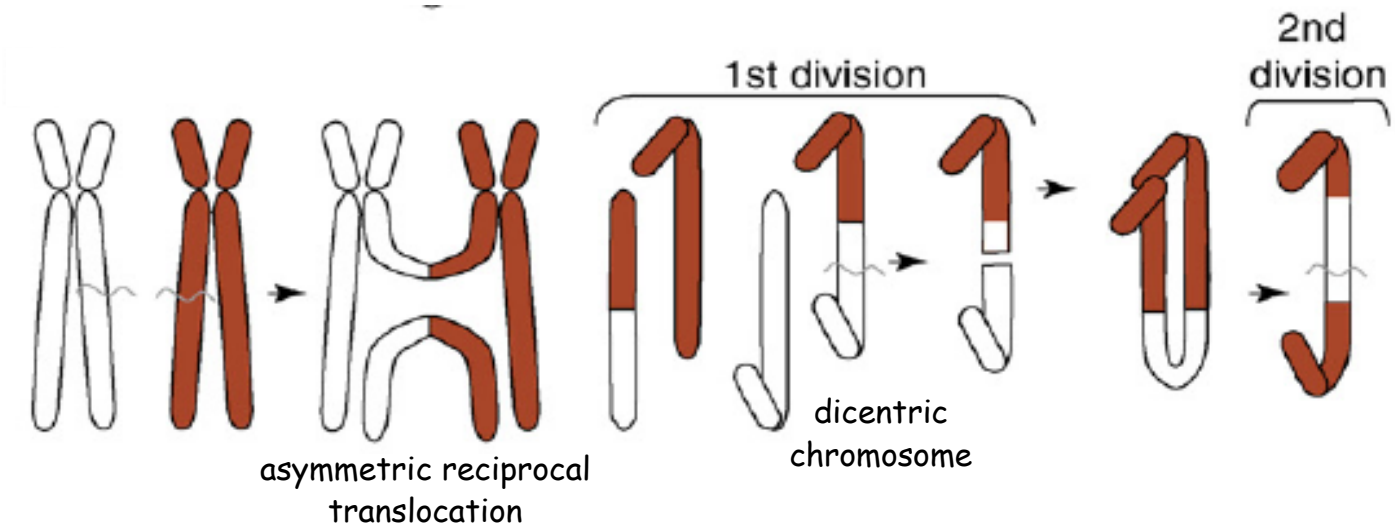
Chromatid type of BFB cycle (chromatid dicentrics)

- has a single centromere at mitotic metaphase
- occurring in post-meiotic mitosis and (after fertilization) in the endosperm
- the chromatid cycle is not found in the maize plant – broken chromosomes delivered to the zygote are healed and become stable (telomeric sequences)

Chromosome type of BFB cycle (chromosome dicentrics)

- two centromeres at mitotic metaphase
- 2 types of orientation at mitosis: criscross and parallel
- criscross (2 centromeres of each chromatid orient to opposite poles; double-bridge configuration in anaphase; both bridges break and the daughter cells receive two broken monocentric chromosomes, the new broken ends in the daughter cells can fuse with each other, forming a dicentric chromosome again)
- parallel (2 centromeres of one chromatid orient to one pole, 2 centromeres of the other chromatid orient to the opposite pole; no bridges)
- in maize, in both the embryo and the endosperm
- double-bridge configuration in young root tips in maize, not in older root tips – chromosome end healing >> stable monocentric chromosomes

Breakage-fusion-bridge cycle (BFB cycle) and chromosomal evolution



- BFB cycles can alter chromosome size and shape via random disruption of dicentric chromatids (which result from asymmetric reciprocal translocation) during anaphase.

- Such disruptions yield deletion, duplication or inversion through fusion of broken ends after replication and another breakage during the next nuclear division (shown only for the upper product of the first bridge). The cycle might stop by healing of breaks when telomeric sequences become attached.