Structural Chromosomal abberations

chromosomal rearrangements

Genetic variation

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

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

Chromosomal aberations/ rearrangements

Chromosomal abberations/ rearrangements

- deletion
- Duplication
- Inversion
- translocation.

Chromosomal abberations/ rearrangements

- For chromosomal rearrangement to occur, there has to be **two or more double-stranded breaks** in the chromosomes of a cell.

- DSBs are potentially **lethal**, unless they are repaired by repair enzymes.

Chromosomal rearrangements

- If the two ends of the **same brea**k are rejoined, the original DNA order is restored.
- If the ends of **two different breaks** are joined together, results in a chromosomal rearrangement.
- The only chromosomal rearrangements that survive meiosis are those that produce DNA molecules that have **one centromere and two telomeres.**

- **acentric chromosome**: Without a centromere
- Do not get dragged to either pole at anaphase of mitosis or meiosis

- Are not incorporated into either progeny nucleus. Therefore acentric chromosomes are not inherited.

Chromosomal rearrangements

Chromosomal Re-arragements

- **Dicentric chromosome**: With two centromere
- pulled simultaneously to opposite poles at anaphase, forming an **anaphase bridge.**
- Generally do not get incorporated into

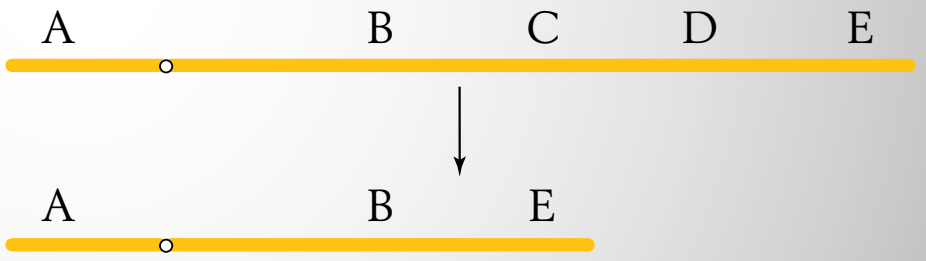
either progeny cell.

Chromosomal Re-arragements

- A chromosome lacking a telomere, cannot replicate properly
- The larger the segment that is lost or duplicated, the more chance, that it will cause phenotypic abnormalities.

Chromosomal Deletions

- **A Kind of Unbalanced rearrangements**
- A **deletion** is the loss of a segment within one chromosome
- they do not revert
- change the gene dosage of a chromosome segment.

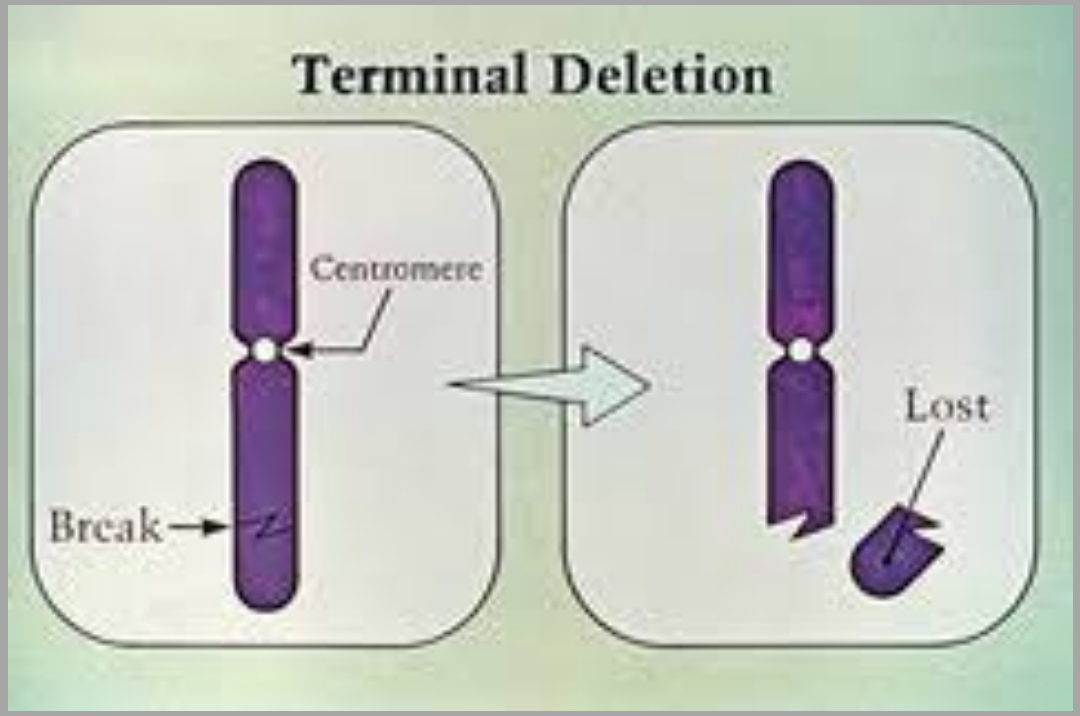


- The effect of a deletion depends on what was deleted.
  - A deletion in one allele of a homozygous wild-type organism may give a normal phenotype
    - while the same deletion in the wild-type allele of a heterozygote would produce a mutant phenotype.
  - Deletion of the centromere results in an acentric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

Deletion Causative Agents

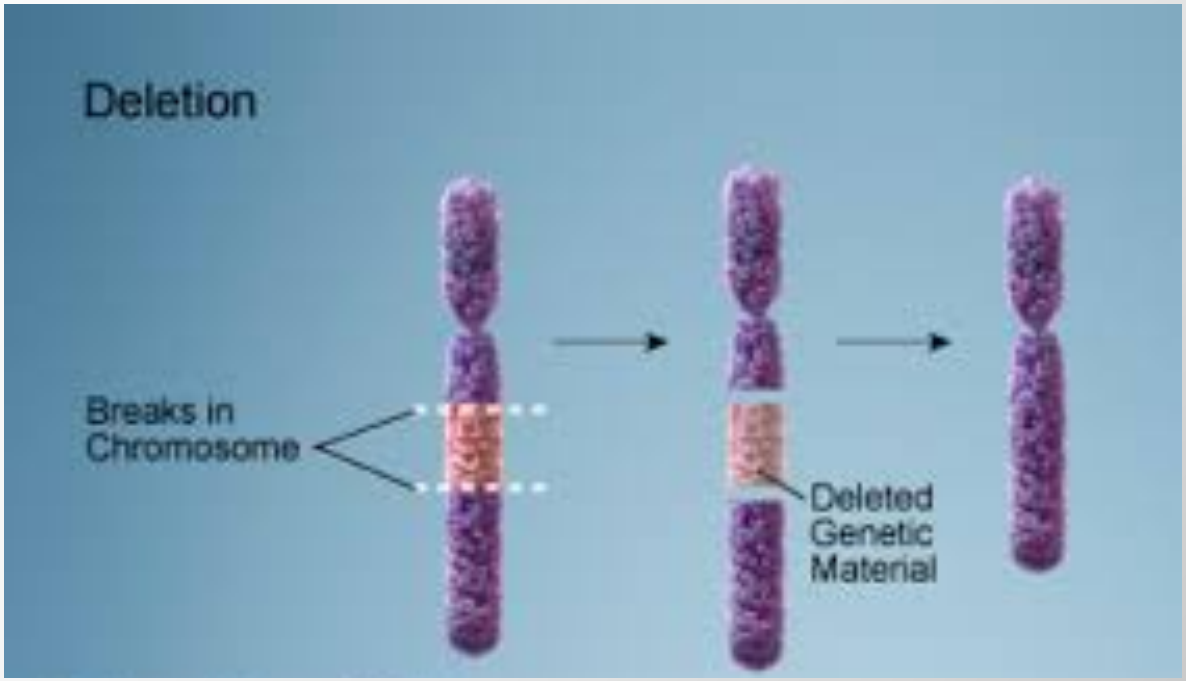
heat	radiation	viruses
chemicals	Transposable elements	errors in recombination

Terminal Deletions



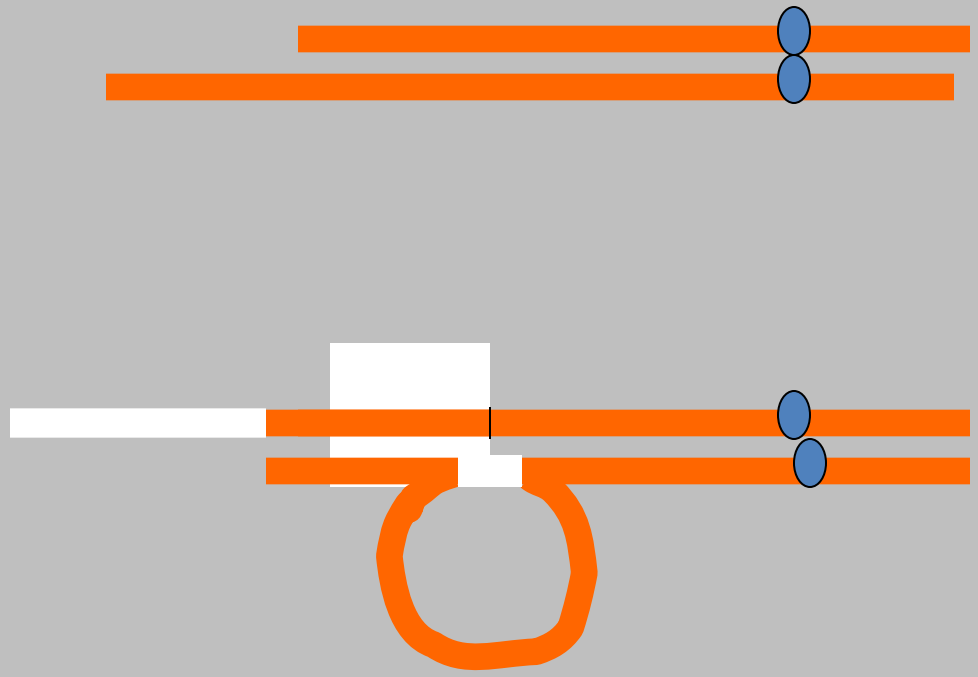
Off the End

Intercalary Deletions



From the Middle

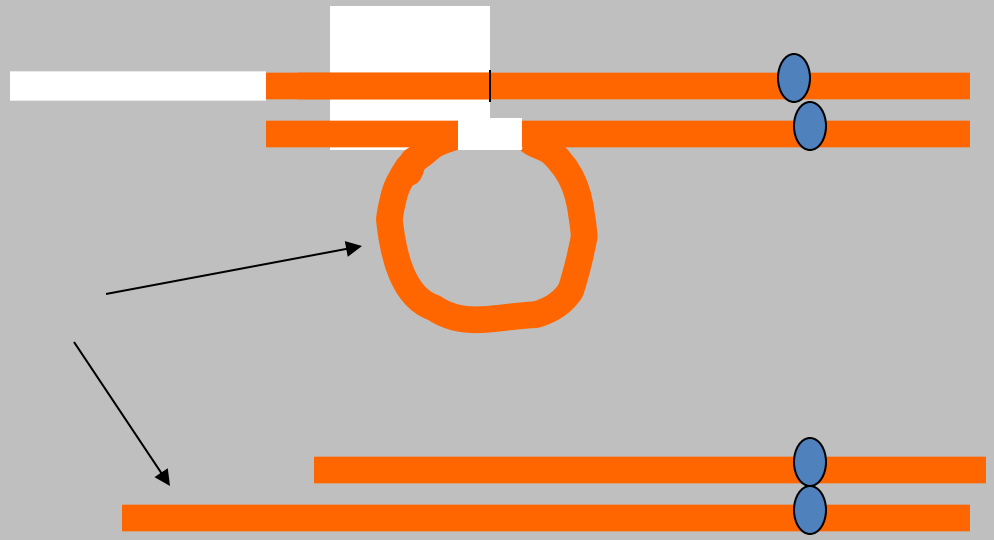
Recognizing Deletions



Terminal

Intercalary

Homologous Pairs?



Intercalary

Hemizygous

Terminal

Hemizygous: gene is present in a single dose.

Deletions

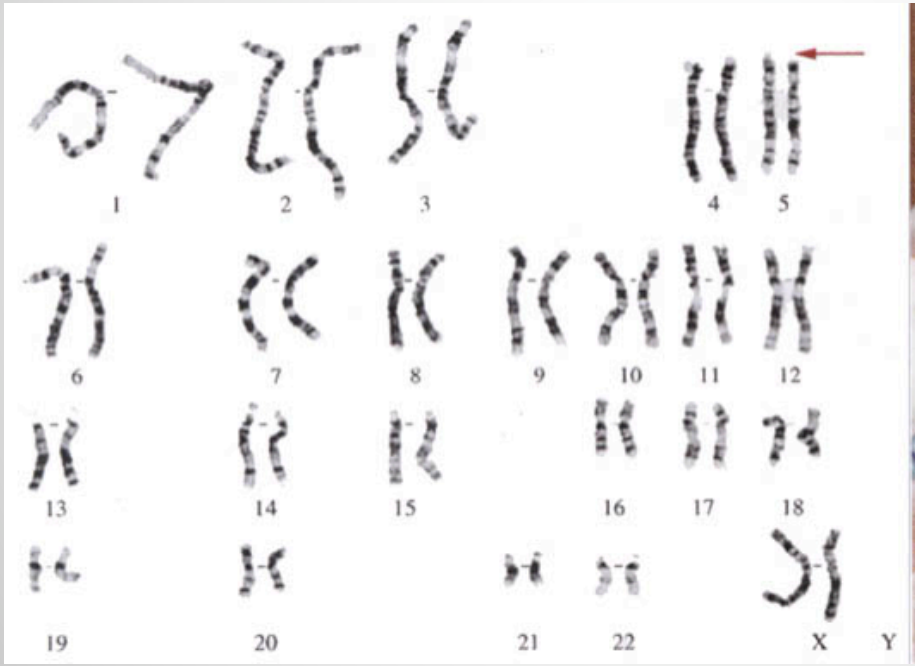
…result in partial monosomy,

…the organism is monosomic for the portion of the chromosome that is deleted

e.g terminal deletion of the small arm (petite arm) of chromosome 5,

Cri-du-chat Syndrome

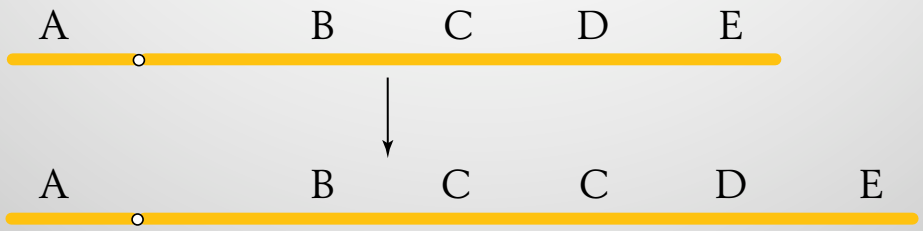
(46, -5p)



Chromosomal Duplication

- A **duplication** is the repetition of a segment of a chromosome arm

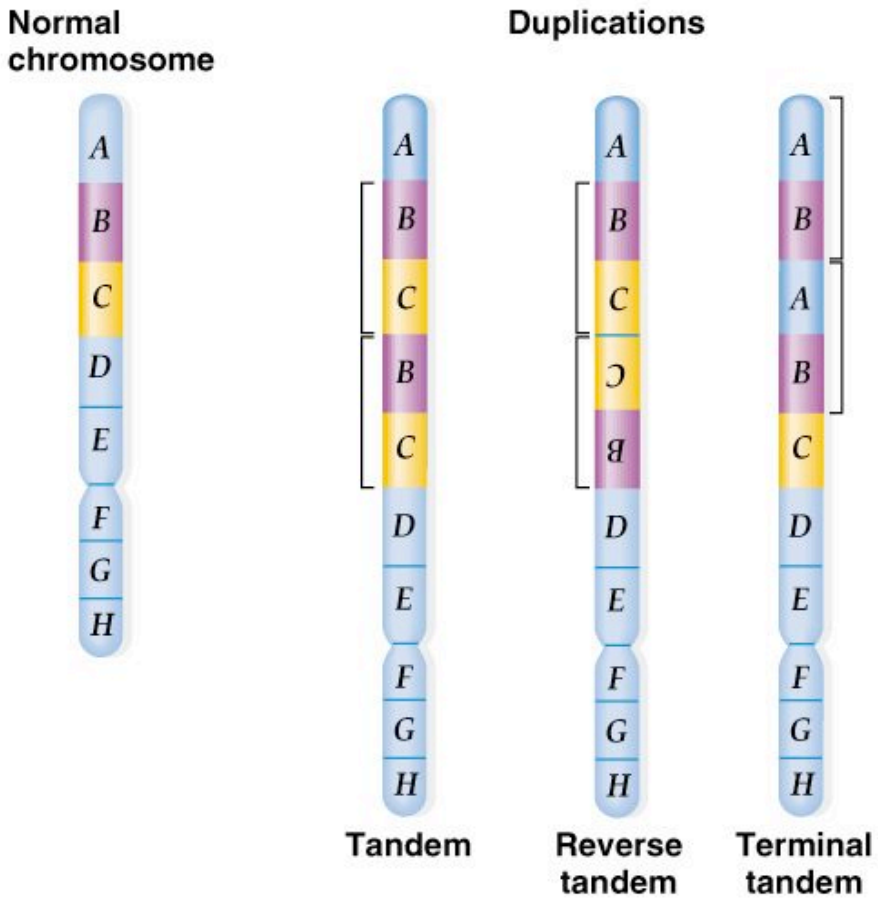
- the duplicate segment can attach at a different position on the same chromosome, or on a different chromosome.



–Tandem duplications are adjacent to each other.

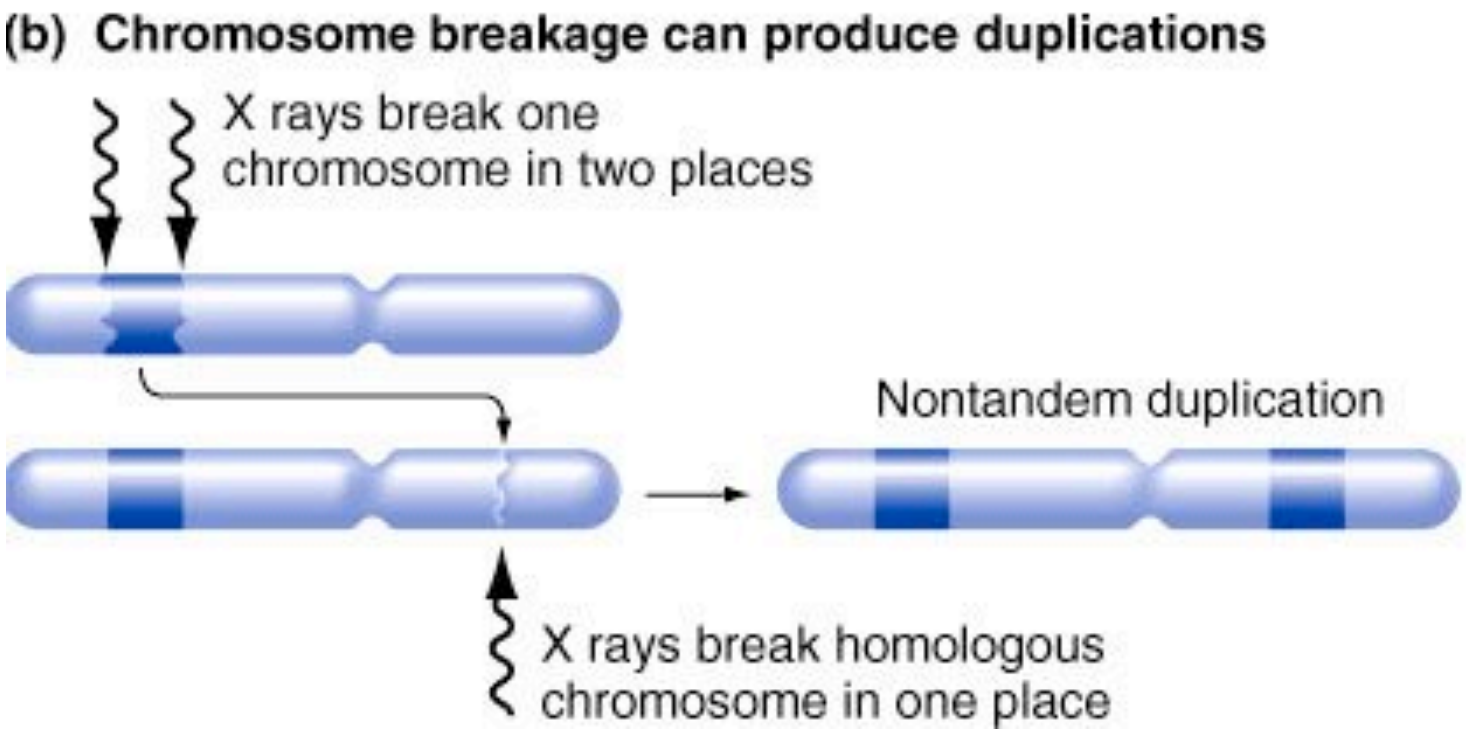
–Reverse tandem duplications result in genes arranged in the opposite order of the original.

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



Duplications

Duplications



etics: Copyright ©

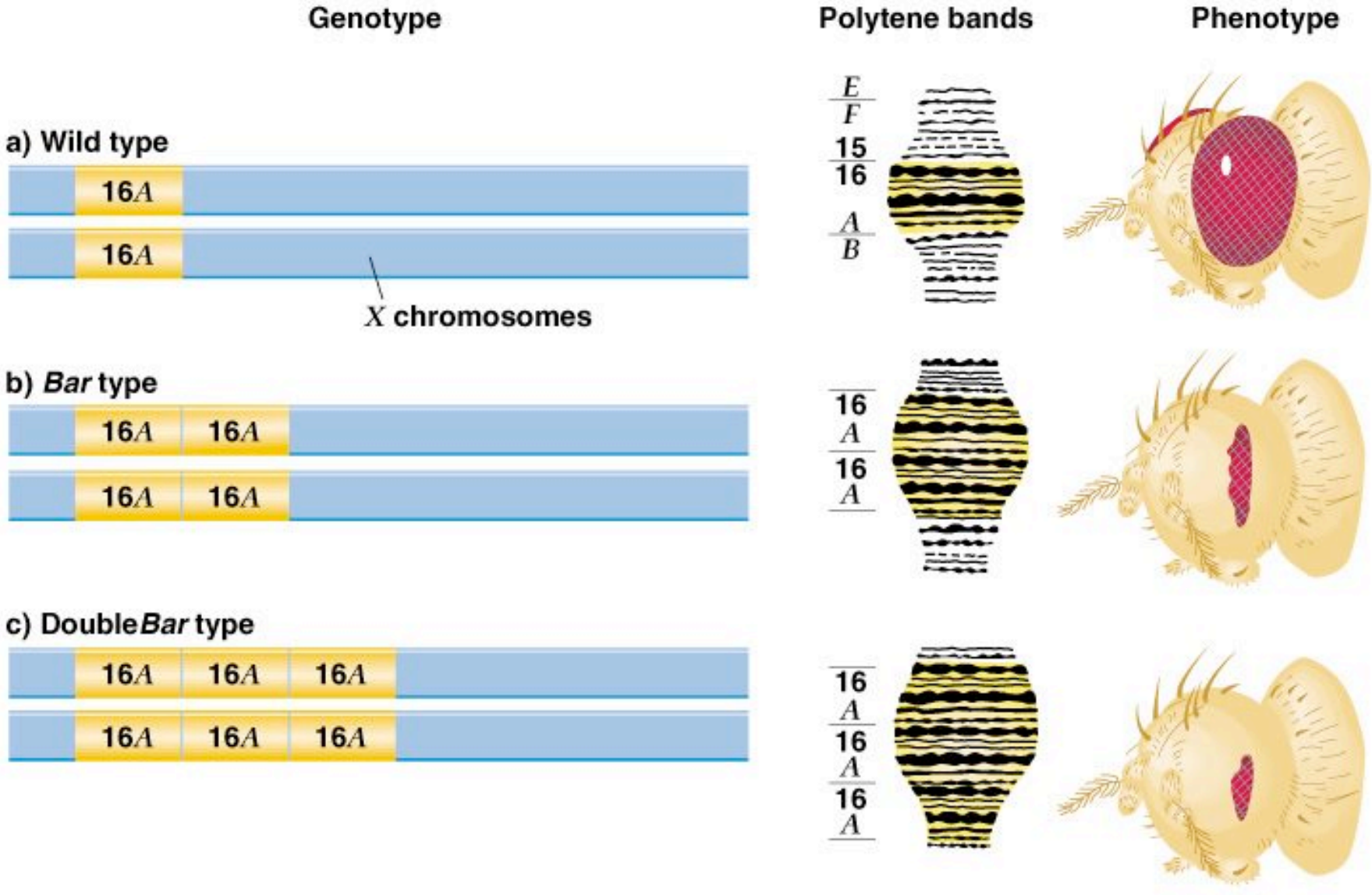
Duplication: example

- Drosophila eye shape allele
  - **Bar**
  - Phenotype: reduces the number of eye facets, giving the eye a slit-like rather than oval appearance
  - The Bar allele resembles an incompletely dominant mutation

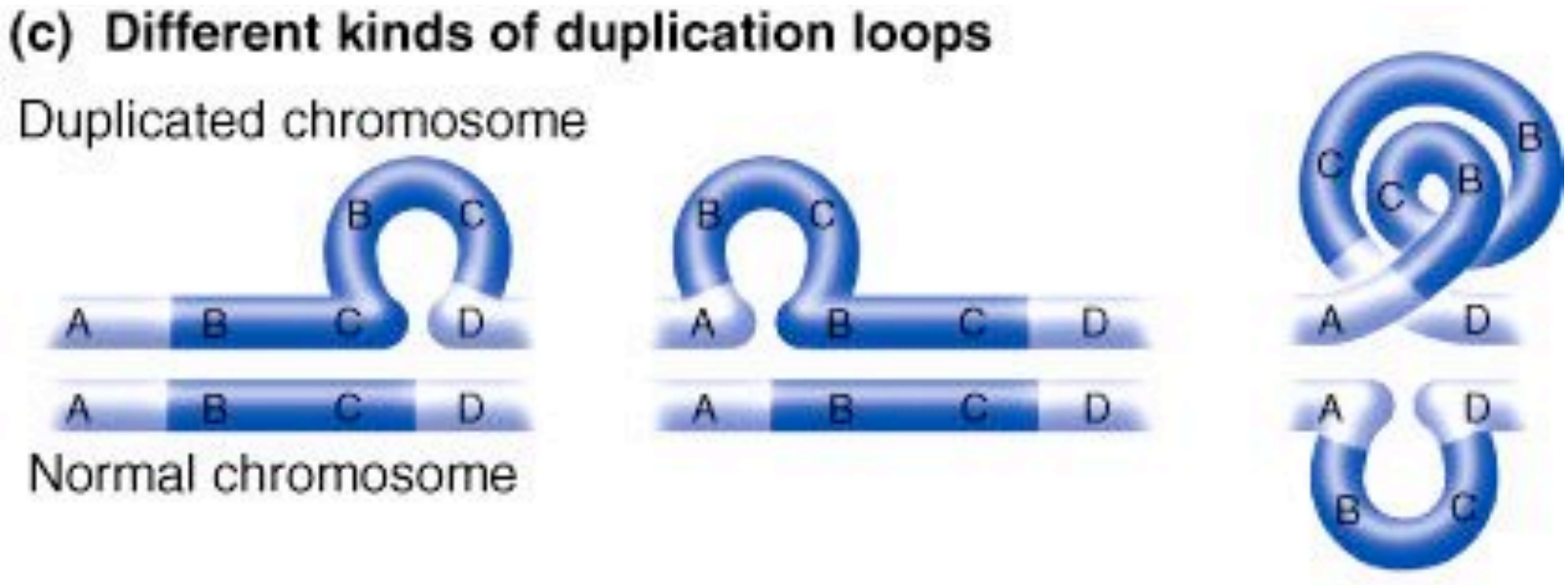
Duplications: example

- Females heterozygous for Bar have
  - a kidney-shaped eye
  - Larger
  - 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

Duplication Cause and Effect

Causes:

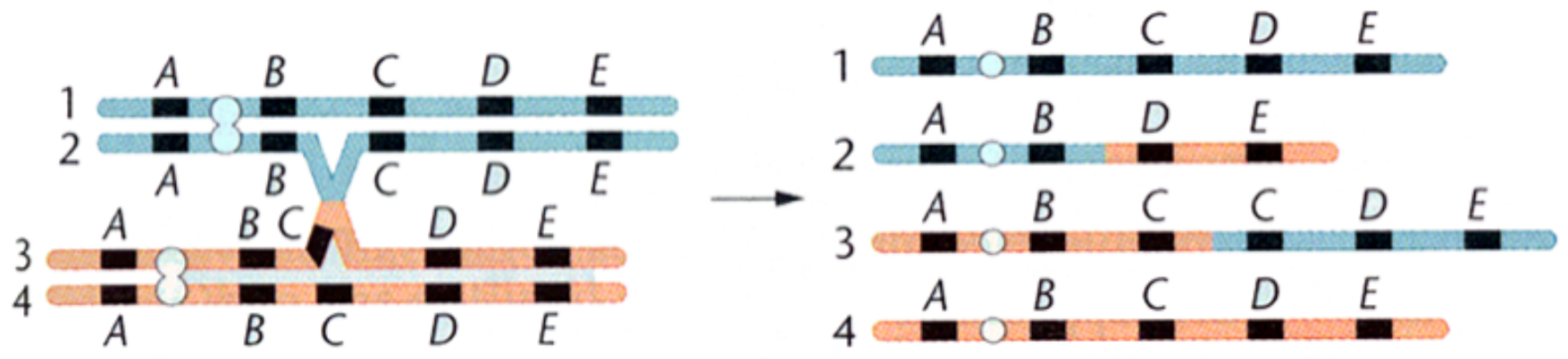
- from unequal crossing over,
- errors in replication during S-Phase.
- X-rays

Effects:

- produces phenotypic variation
- an important source for genetic variability during evolution.

Unequal Crossing Over

Produces both duplications and deletions!



Chromosomal Inversions

Aberrations in which a portion of the chromosome is turned around 180°.

Inversions are of two basic types:

- Paracentric
- Pericentric

Inversions

- Inversions are also called balanced rearrangements
  - As there is no change the overall amount of genetic material, hence no gene imbalance.

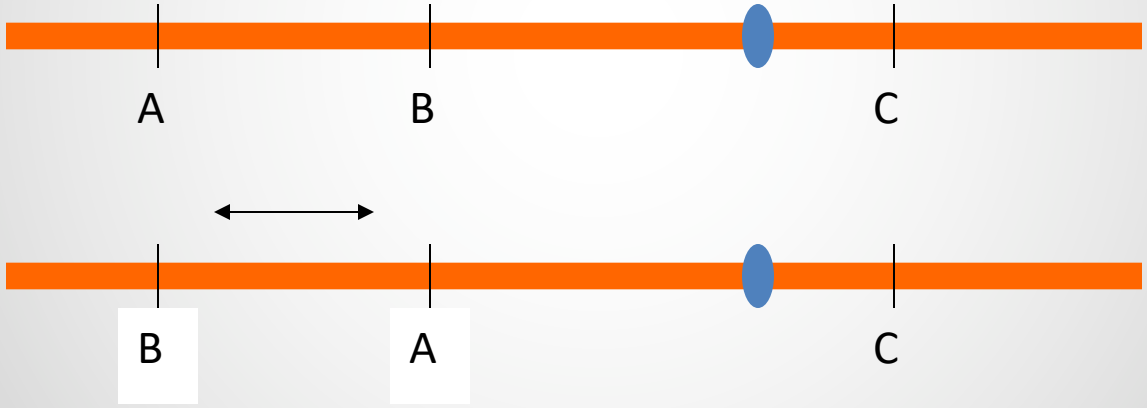
Inversions

- Individuals with inversions are generally **normal**, if there are no breaks within genes.

- A break that disrupts a gene may produce a mutation that may be detectable as an abnormal phenotype.

1. Paracentric Inversion

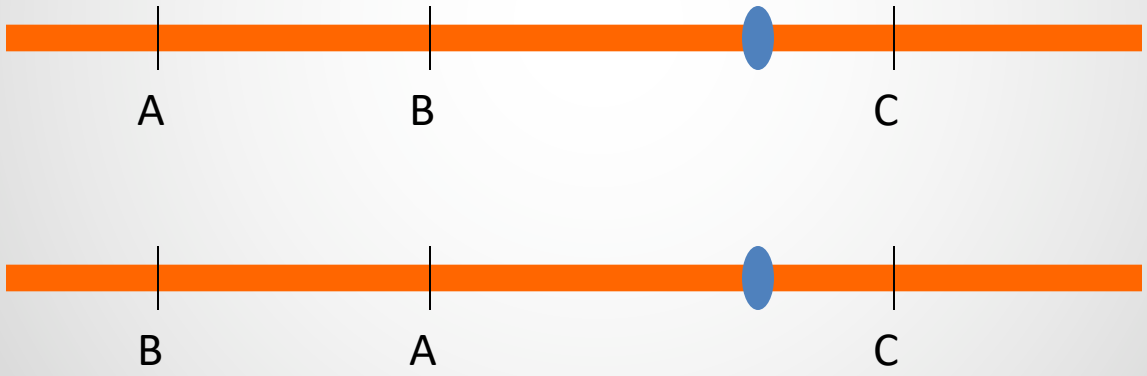
...an inversion in which the centomere is <u>not</u> included,



...Hence, a paracentric inversion does not change arm length ratio.

Inversion Heterozygotes

…an organism with one wild-type and one chromosome containing an inversion,



…<u>not</u> heterozygous for the genes, heterozygous for the chromosomes.

Inversions: Common observations

- Linked genes are often inverted together.
- The meiotic consequence of inversion depends on whether it occurs in a homozygote or a heterozygote.
- A homozygote will have normal meiosis.

Inversions

- The effect in a heterozygote depends on whether crossing-over occurs or not
  - If there is no crossing-over, no meiotic problems occur.
  - If crossing-over occurs in the inversion, unequal crossover may produce serious genetic consequences.

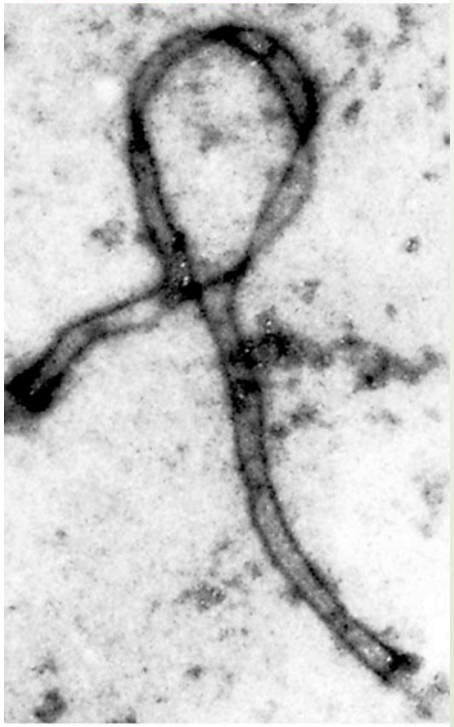
inversion heterozygote

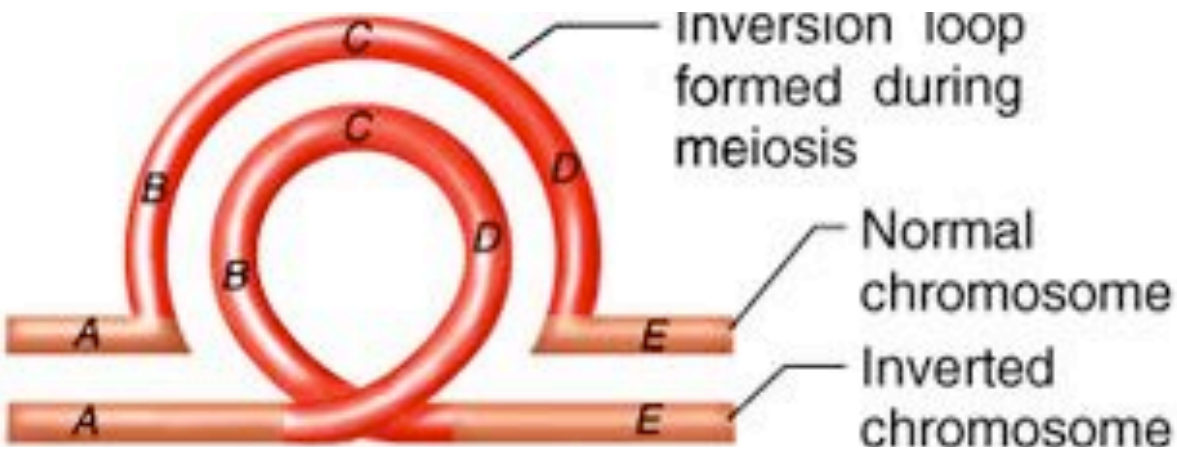
- The location of the inverted segment can be detected microscopically.

- During meiosis, one chromosome twists once at the ends of the inversion to pair with the other untwisted chromosome; in this way the paired homologs form a visible **inversion loop**

Inversion heterozygotes reduce the number of recombinant progeny

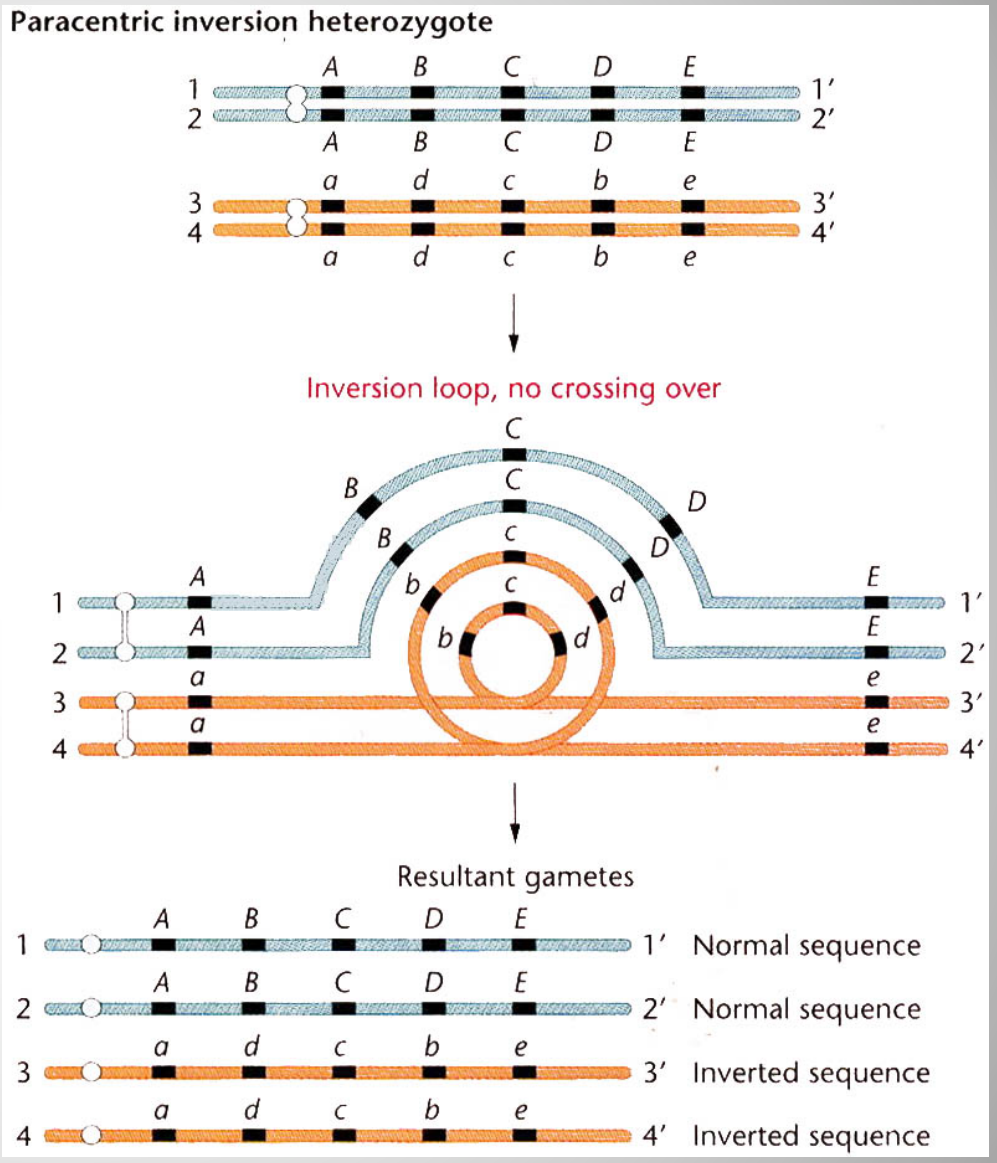
- Inversion loop in heterozygote forms tightest possible alignment of homologous regions



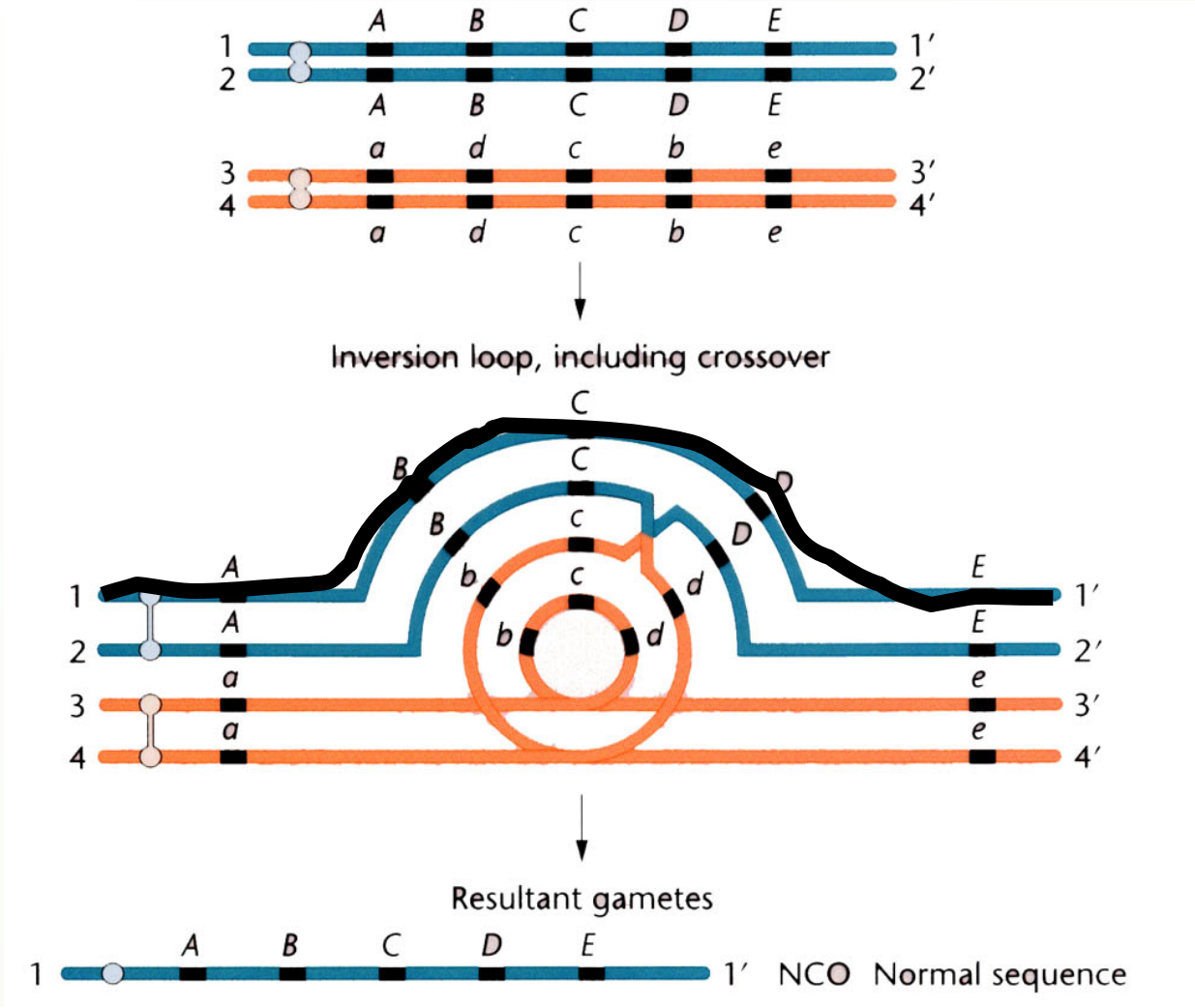


Inversion Loop

no crossing over

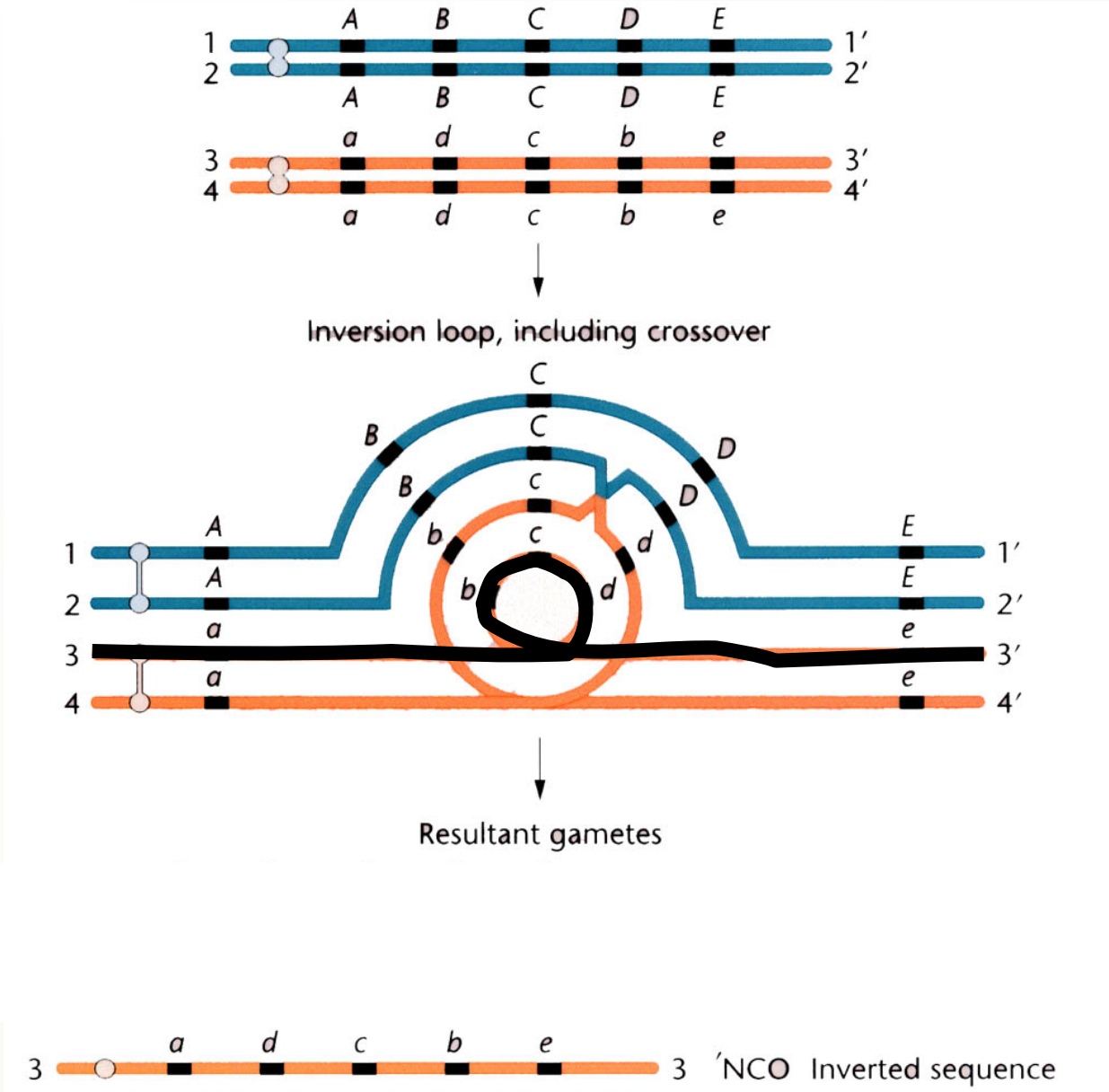


Paracentric



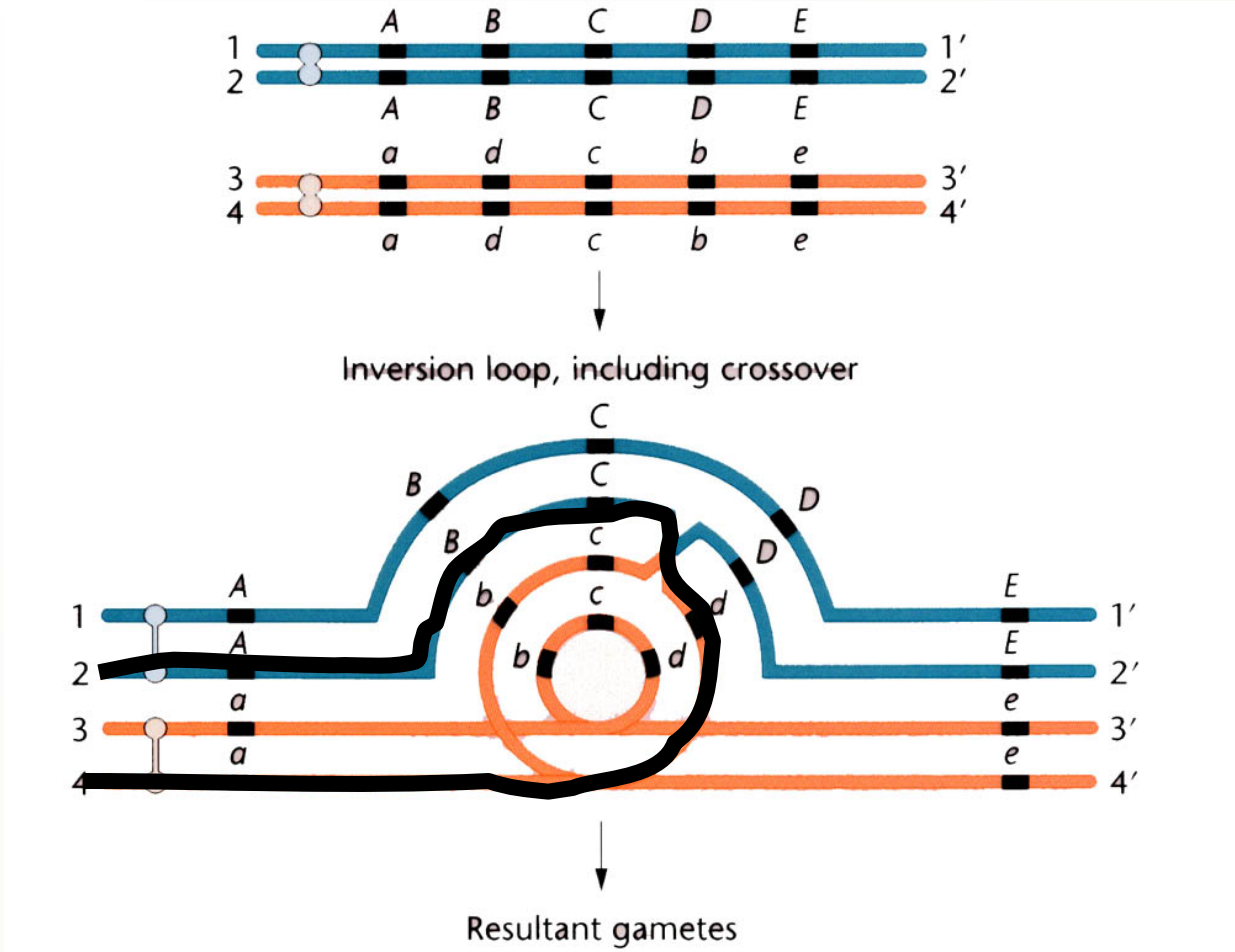
Produces haploid gamete.

Paracentric



Produces gamete with inversion.

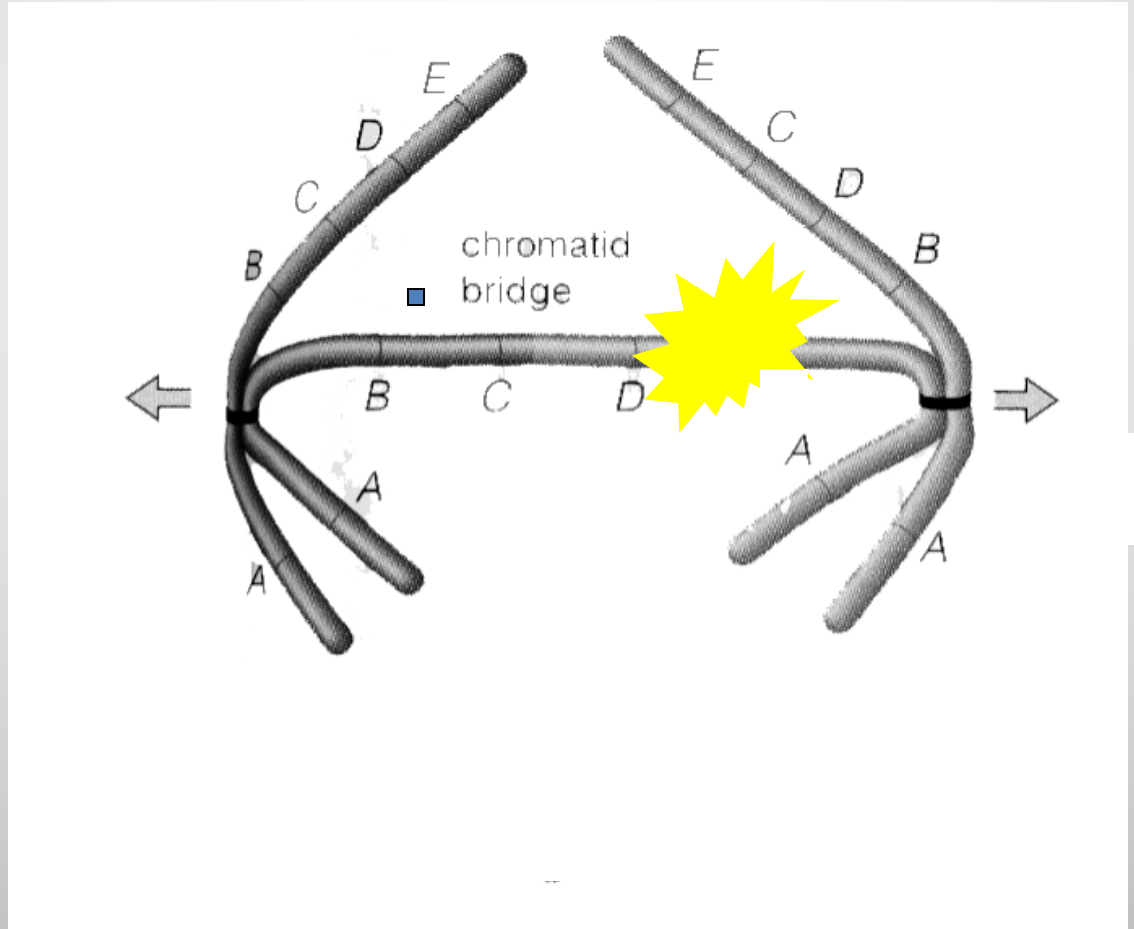
Paracentric



Produces a chromosome with two centromeres.
Nonviable gametes.

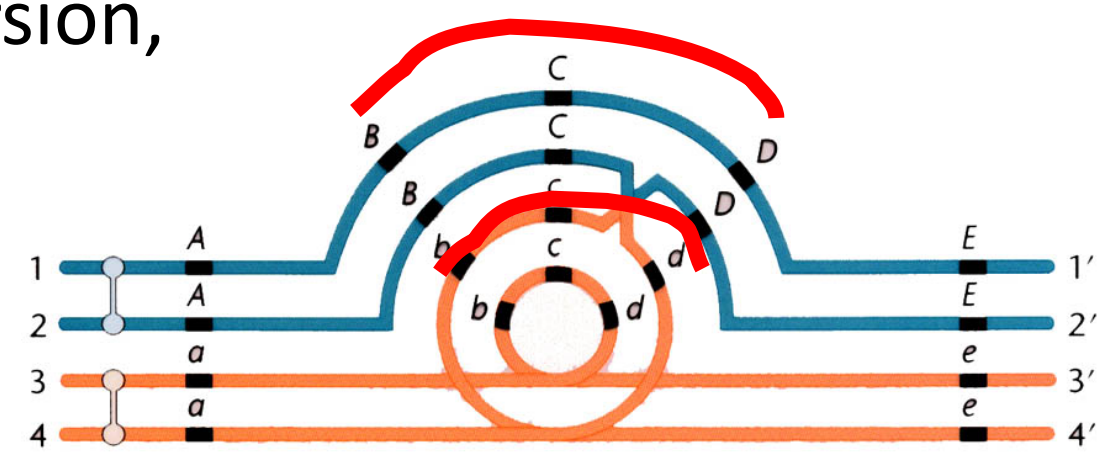
Dicentric

...a chromosome having two centromeres;

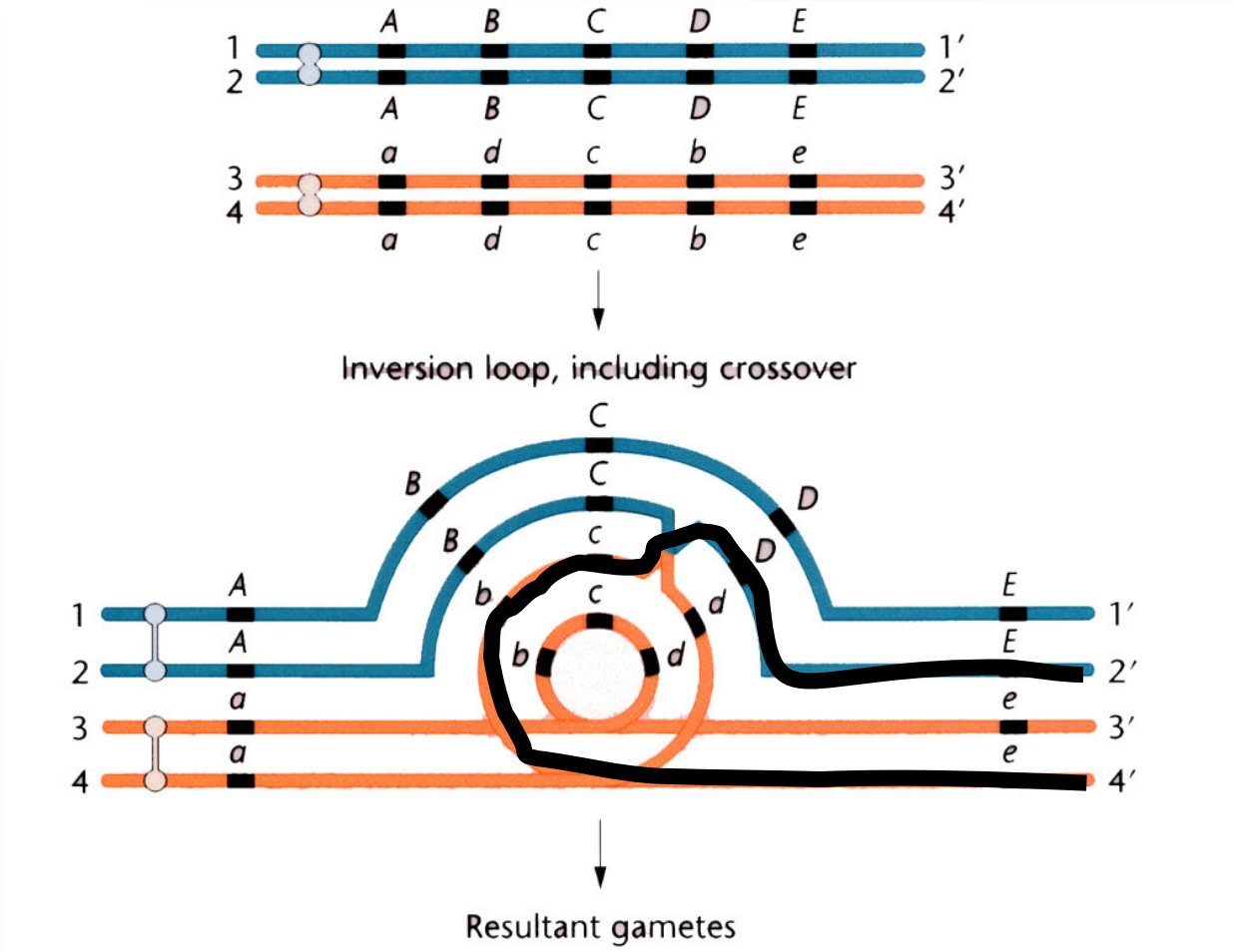


Dicentric

…results only when the crossing over occurs within the region of the paracentric inversion,



Paracentric



No centromeres. Deletions.

Nonviable gametes.

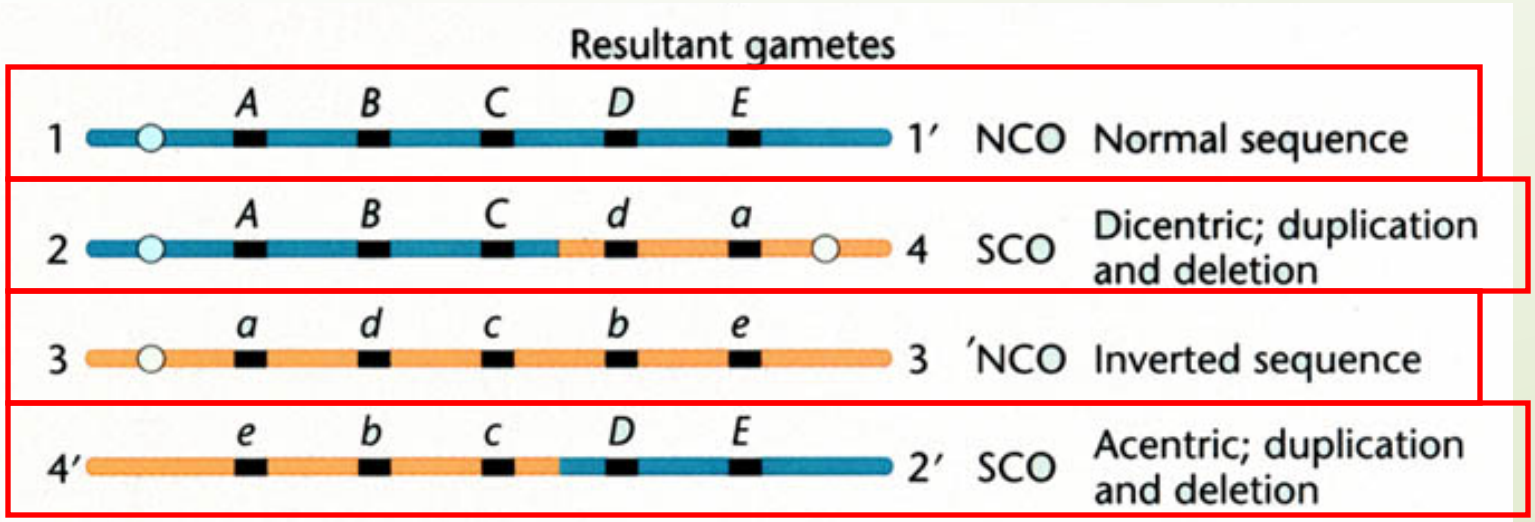
Acentric

…a chromosome having no centromeres,

…segregates to daughter cells randomly, or is lost during cell division,

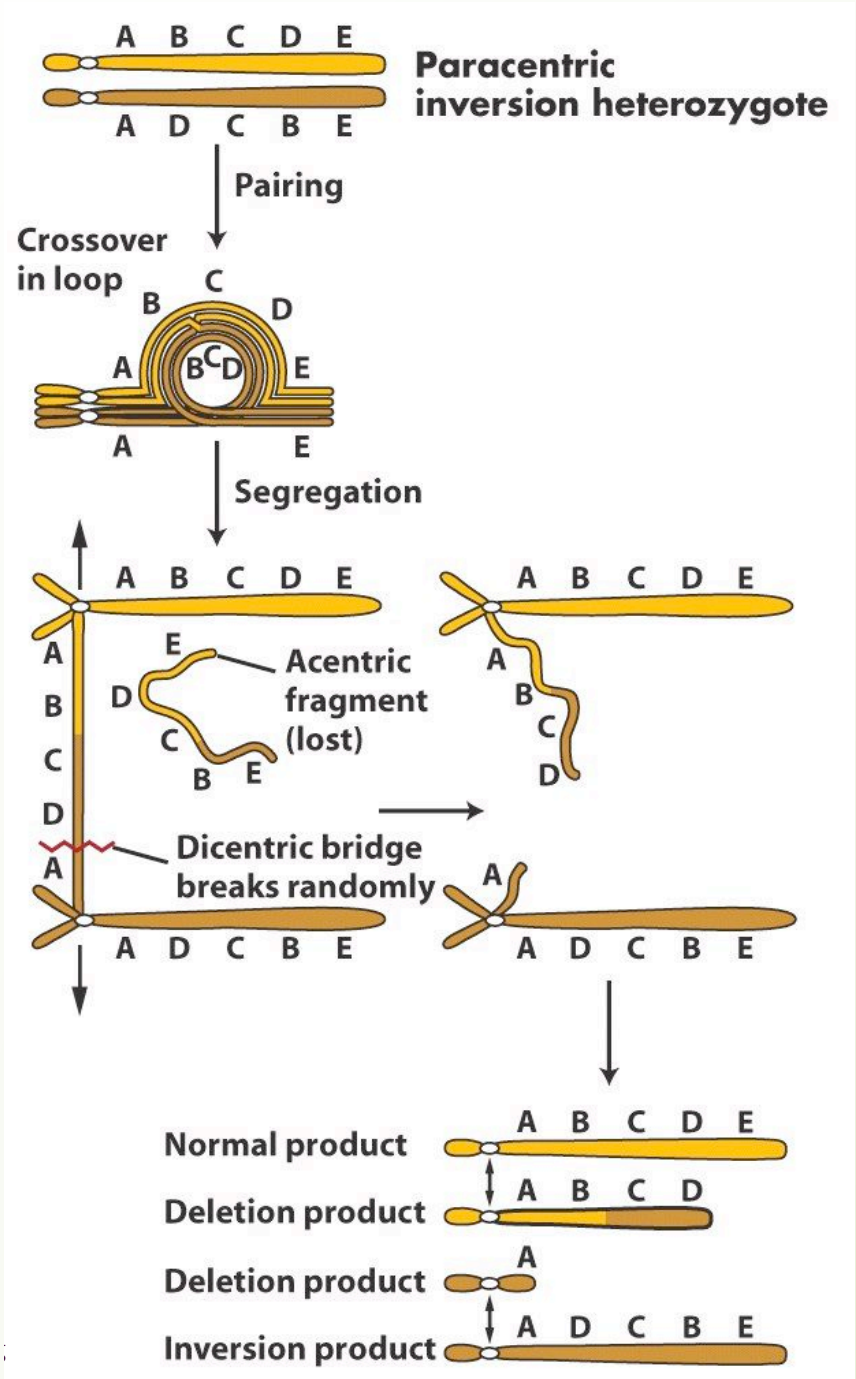
…deletions impart partial monosomy.

Paracentric Outcomes



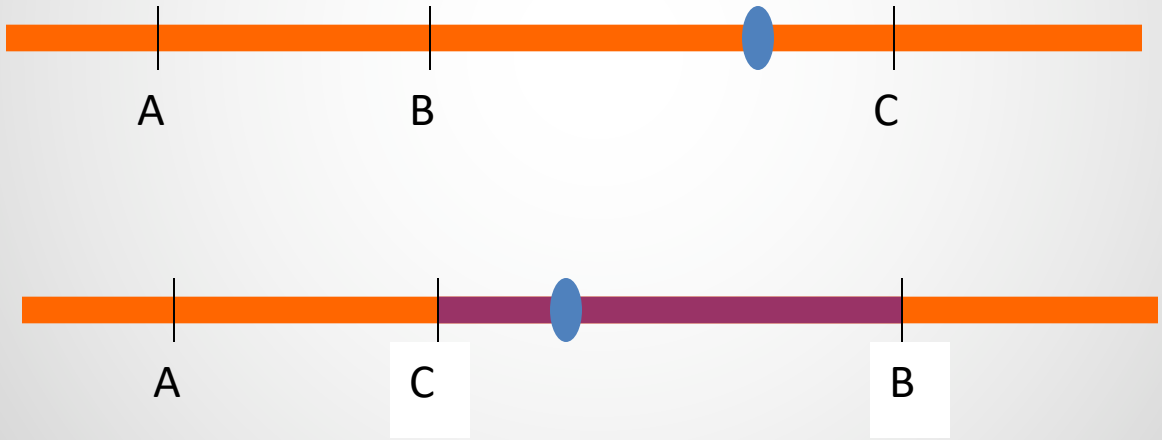
1 Normal Gamete, 1 Inversion Gamete, **No Crossover Classes**

Recombination is not inhibited, but recombinant gametes are selected against.


A B C D E
A D C B E
Paracentric inversion heterozygote
Pairing
Crossover in loop
Segregation
Acentric fragment (lost)
Dicentric bridge breaks randomly
Normal product
Deletion product
Deletion product
Inversion product

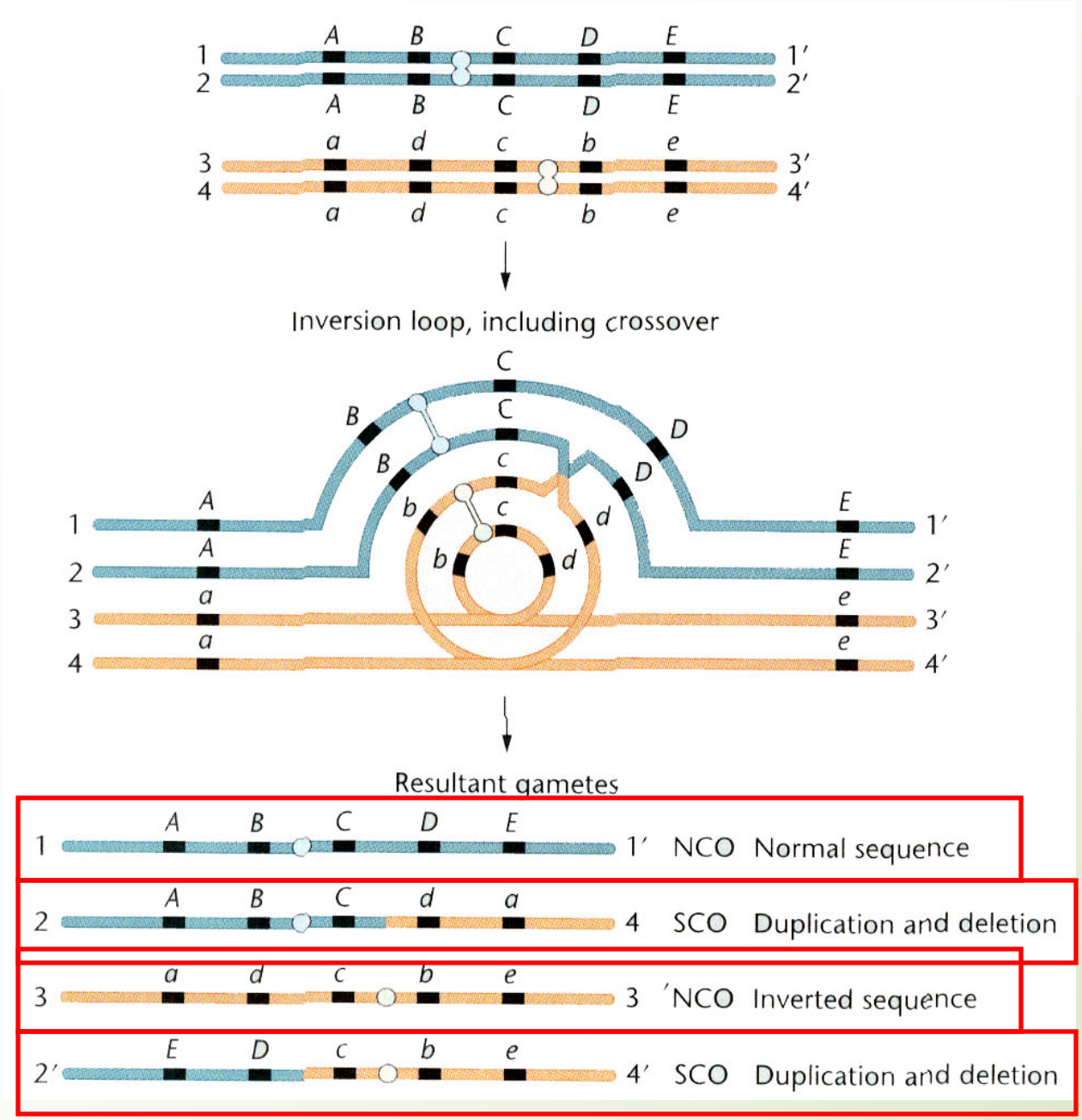
2. Pericentric Inversion

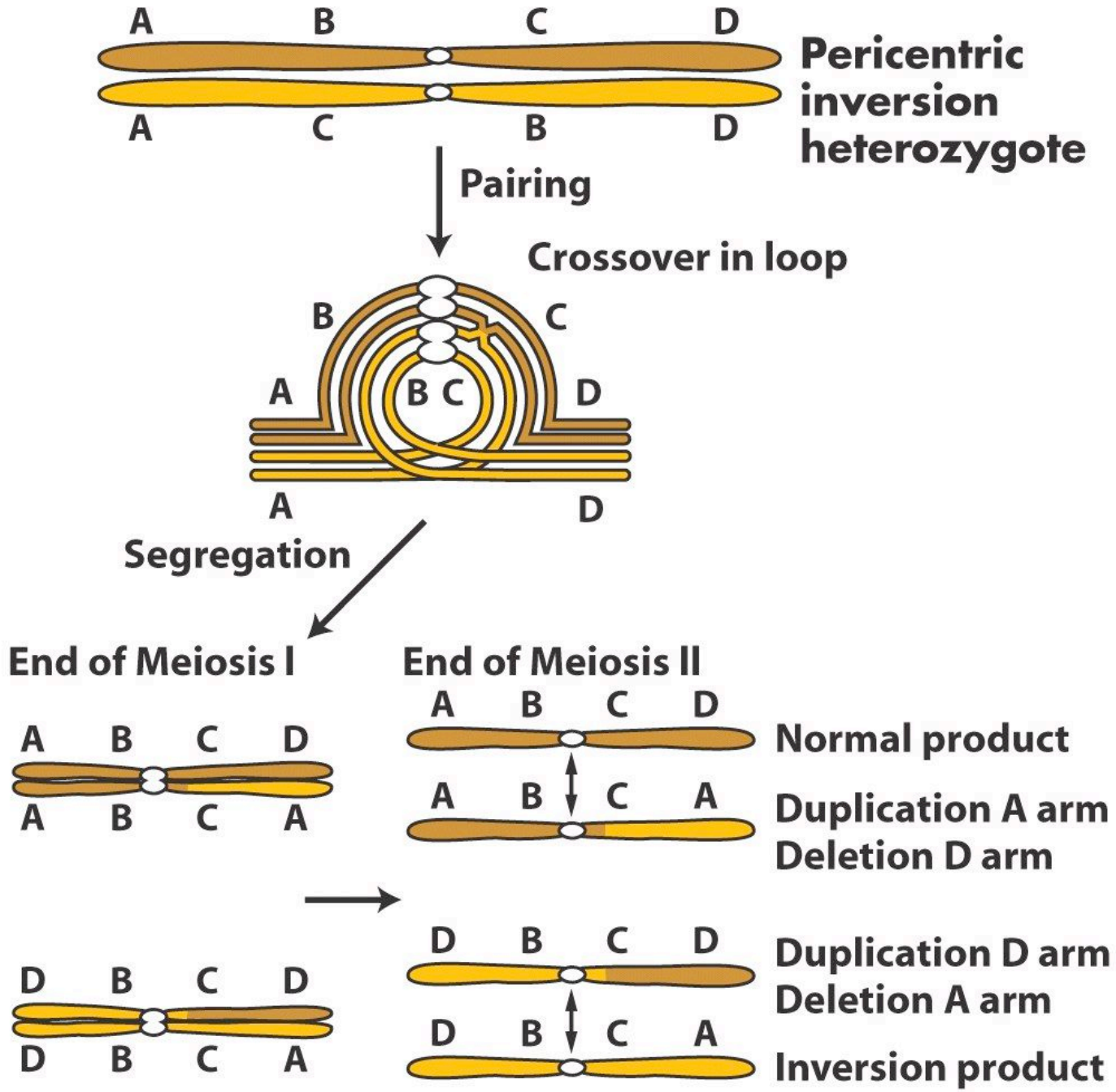
...an inversion in which the centromere is included,



...a pericentric inversion results in a change in chromosome arm length.

Pericentric




A B C D
A C B D
Pericentric inversion heterozygote
Pairing
Crossover in loop
B C
A B C D
A D
Segregation
End of Meiosis I
End of Meiosis II
A B C D
A B C A
A B C D
Normal product
A B C A
Duplication A arm
Deletion D arm
D B C D
D B C A
D B C D
Duplication D arm
Deletion A arm
D B C A
Inversion product

Recombination and Inversions

- Paracentric and Pericentric;
  - 1 Normal Gamete,
  - 1 Inverted Gamete,
  - No Crossover Classes = **No Recombination,**

Inversions select against recombinant gametes, thus preserves co-segregation of specific alleles.

Inversion

- In an inversion, the total amount of genetic information stays the same therefore most have no phenotypic consequences

- In rare cases, inversions can alter the phenotype of an individual due to
  - **<u>Breakpoint effect</u>: The breaks leading to the inversion occur in a vital gene.**

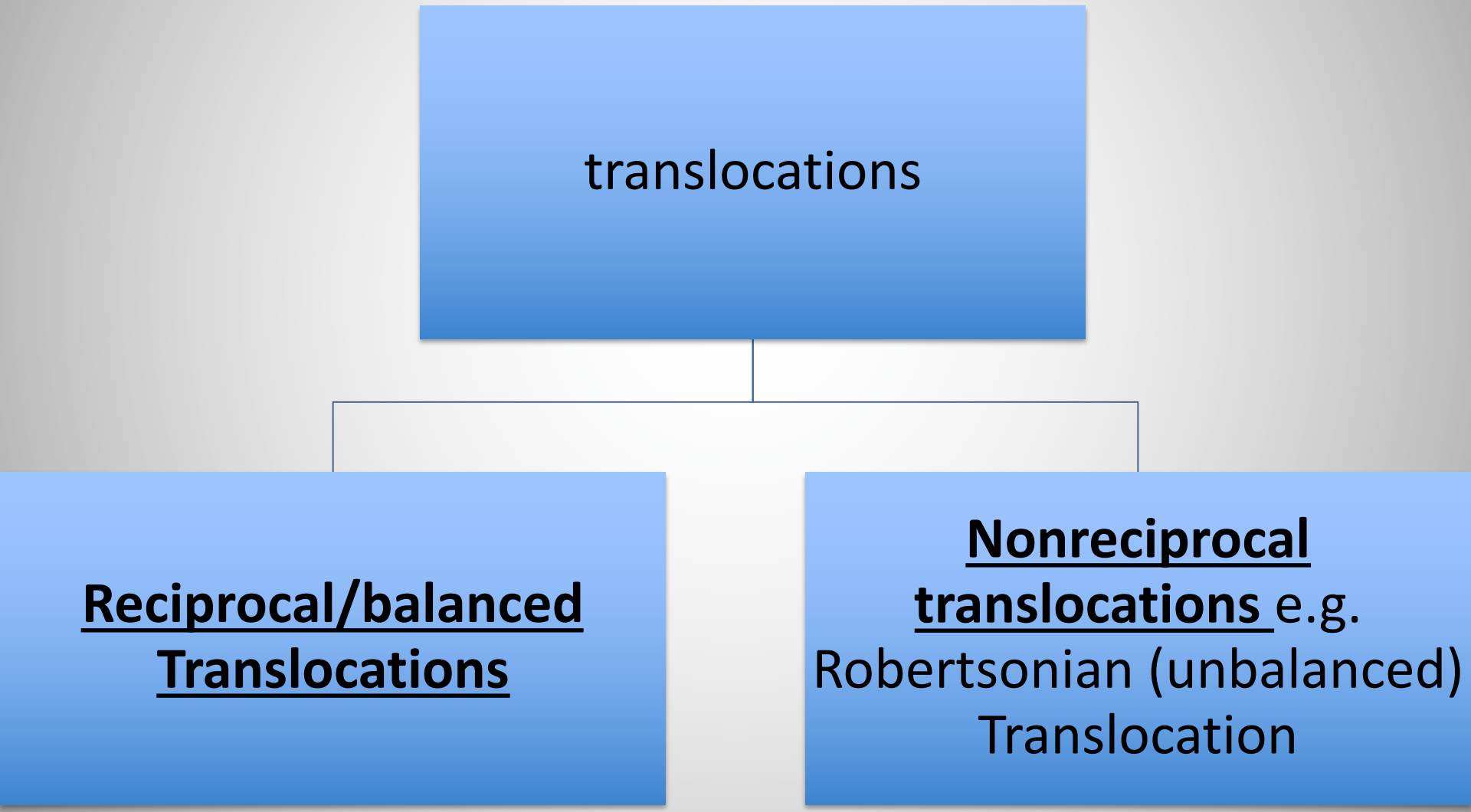
  - **<u>Position effect</u>: A gene is repositioned in a way that alters its gene expression.**

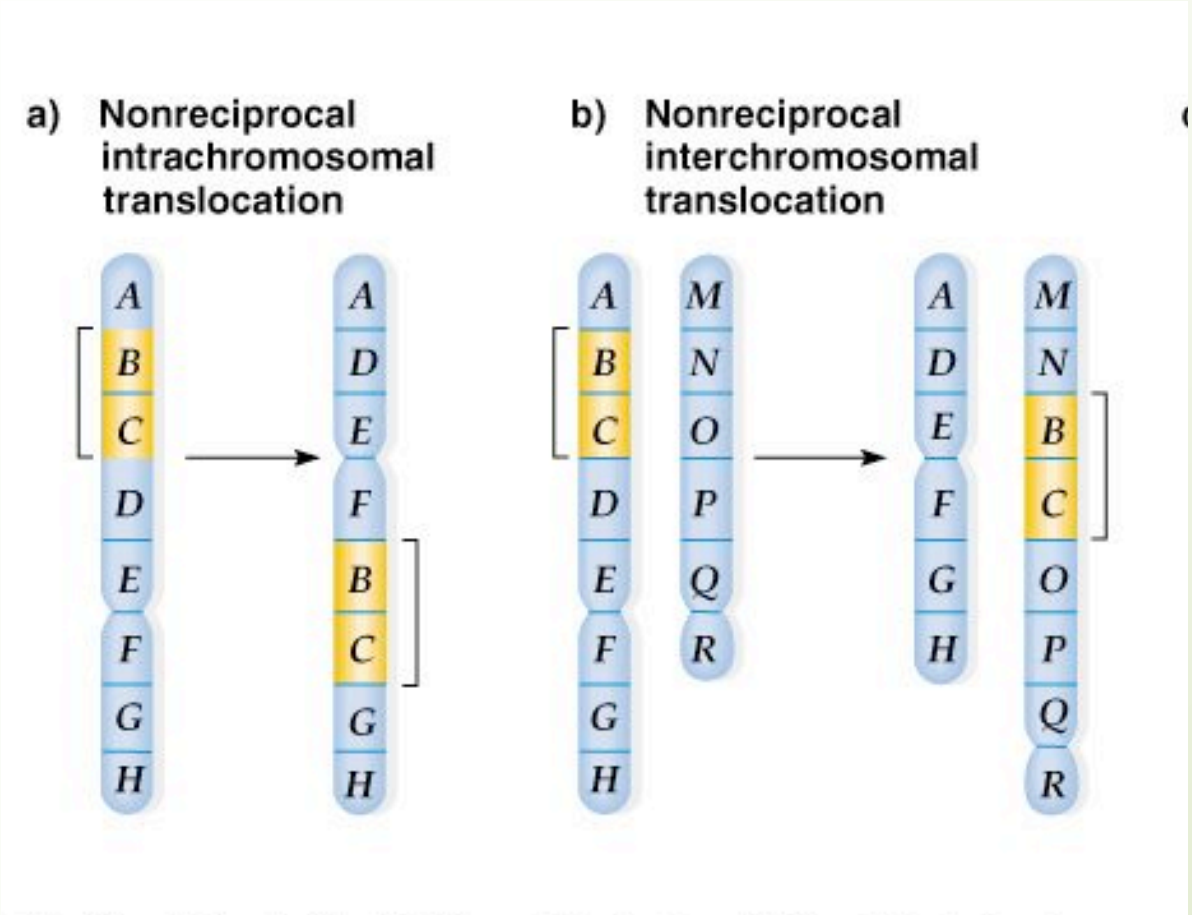
Inversions and Evolution

- Inversions 'lock' specific alleles together,
  - all offspring get the alleles from either a wild-type, or inverted chromosome,
- If the 'set of alleles' is advantageous, the set can be maintained in the population.
- About 2% of the human population carries inversions that are detectable with a light microscope

Translocations

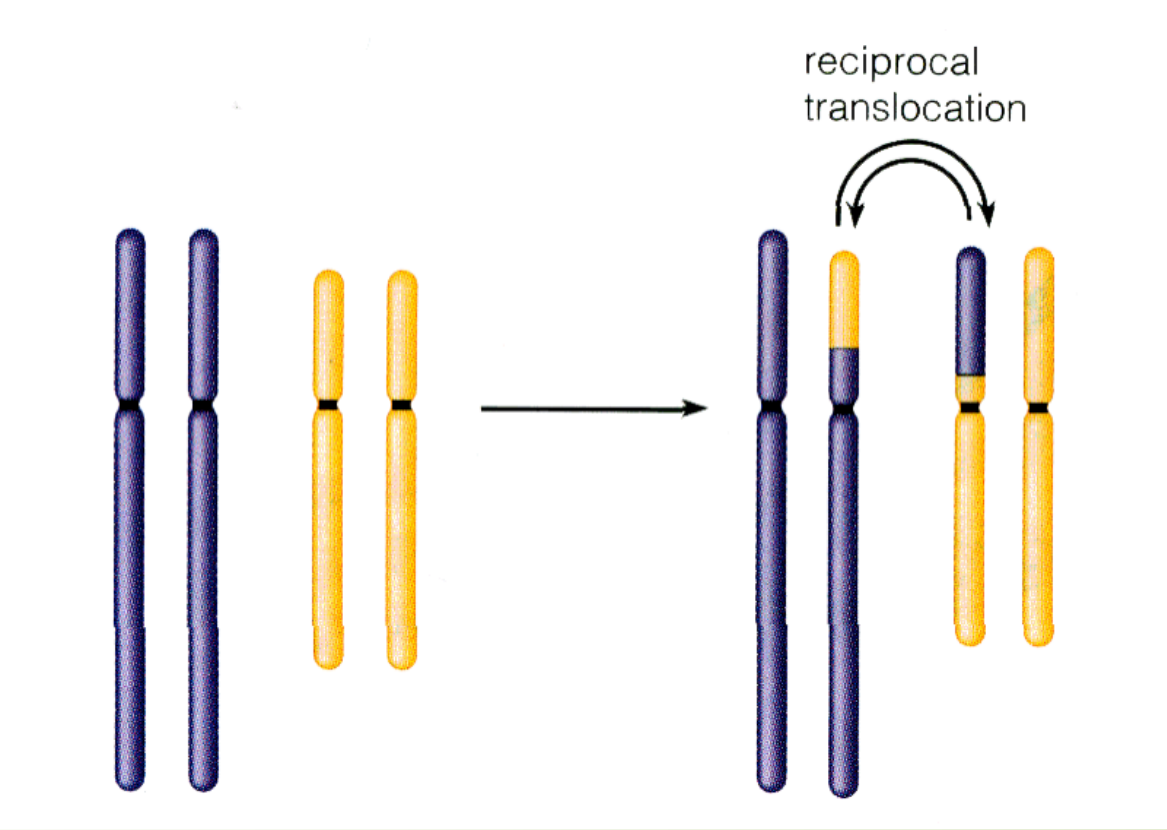
aberration associated with the transfer and attachment of a chromosomal segment to a new location in the genome


translocations
Reciprocal/balanced Translocations
Nonreciprocal translocations e.g. Robertsonian (unbalanced) Translocation

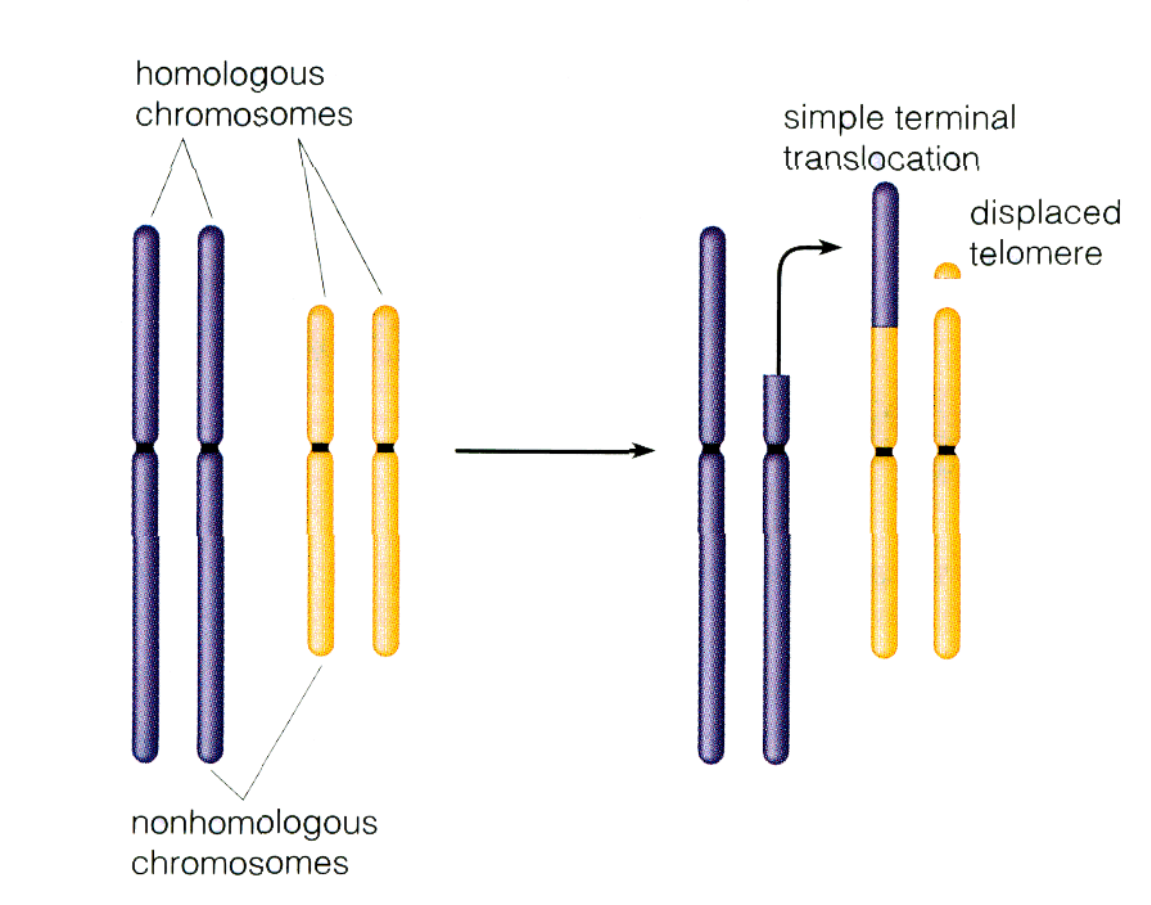


Both types of translocations are capable of causing disease in humans.

Reciprocal Translocation

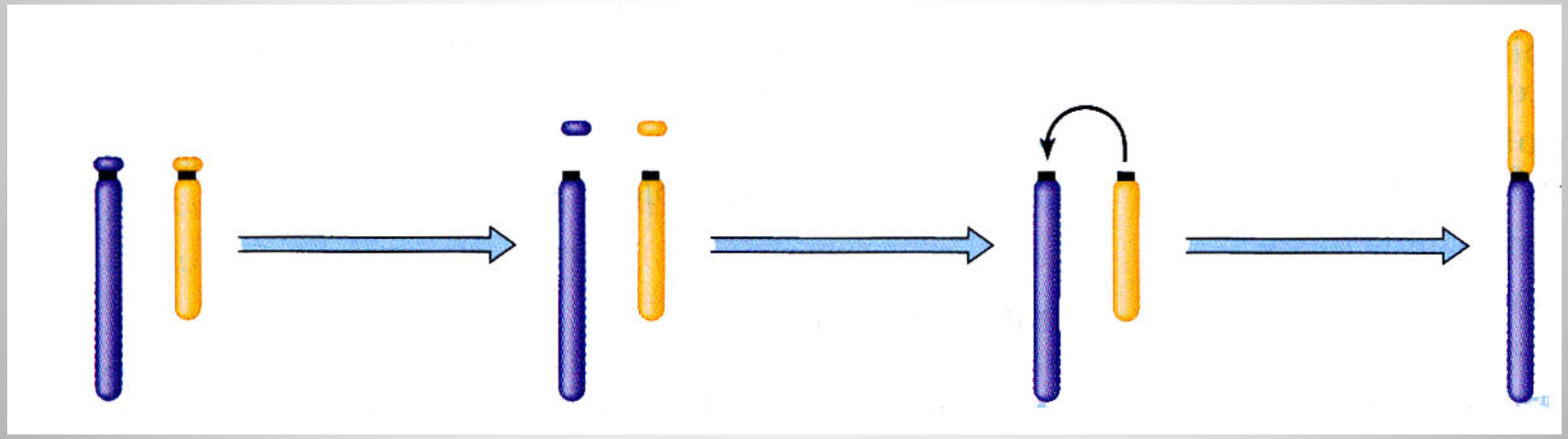


Terminal Translocation



Robertsonian Translocations

resulting in the fusion of long arms of acrocentric chromosomes,



Robertsonian translocation

- Breaks occur at the extreme ends of the short arms of two non-homologous acrocentric chromosomes
- The larger fragments fuse at their centromeric regions to form a single chromosome
- The small acrocentric fragments are subsequently lost.

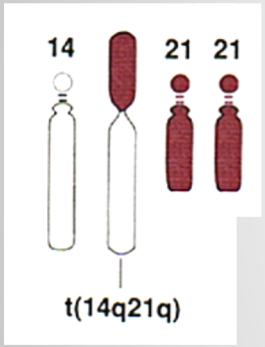
Robertsonian translocation

- This type of translocation is the most common type of chromosomal rearrangement in humans.

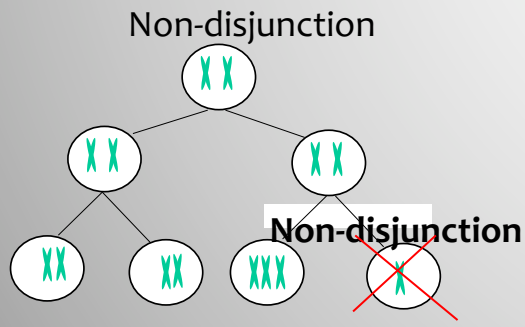
- Robertsonian translocations are seen in human chromosomes 13, 14, 15, 21 the acrocentric chromosomes

Three ways leading to Down syndrome

- 95% people have three separate copies of chromosome 21 - **trisomy 21**



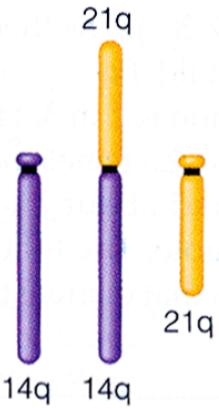
- 4% have the extra copy of chromosome 21 because of a **translocation (Familial down syndrome)**



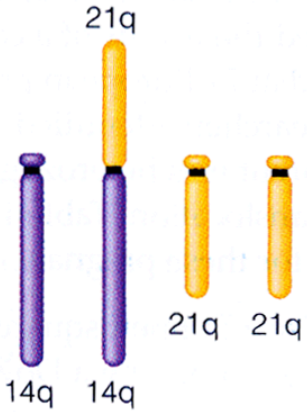
- 1% have **mosaicism** with normal and trisomy 21 cell lines (and usually have much milder features because of the presence of the normal cells); - occurs post zygotically

Familial Down Syndrome

a Normal karyotype: two copies of 14q, two copies of 21q.

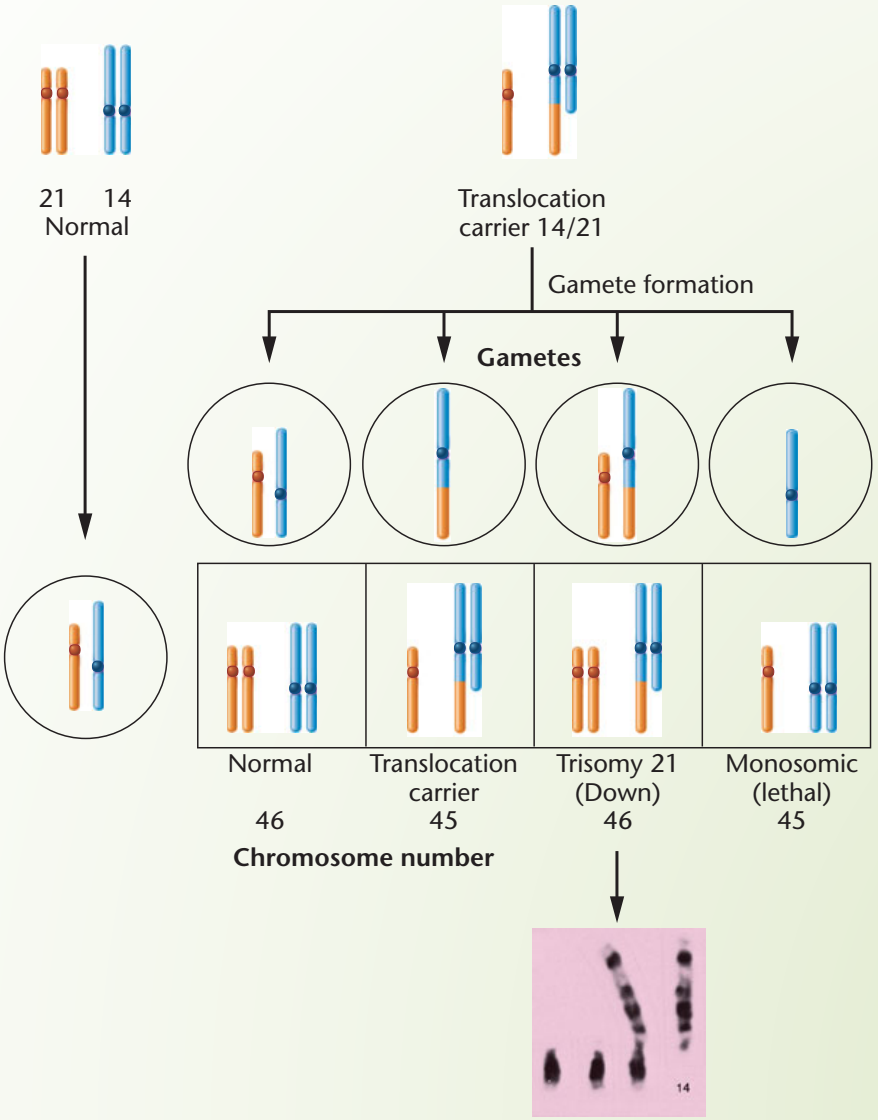


b Balanced translocation carrier: two copies of 14q, two copies of 21q.



c Translocation Down syndrome (trisomy 21q): two copies of 14q, three copies of 21q.

Familial Down Syndrome



Translocations: Features

- Two different, non-homologous chromosomes are broken and rejoined to each other.

- All the genes are present, so an individual with a translocation can be completely normal.

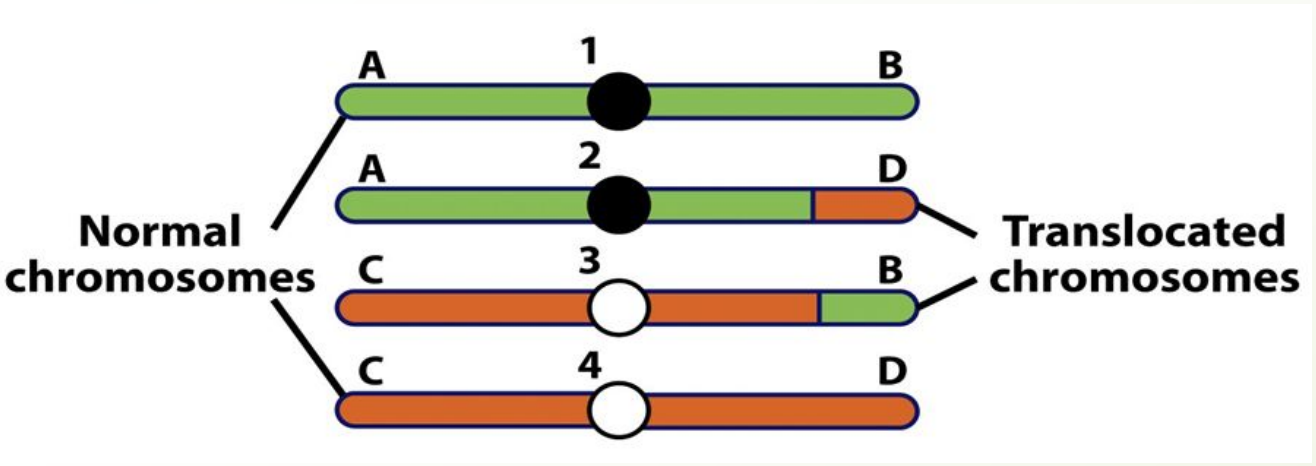
- an individual heterozygous for a translocation can have fertility problems

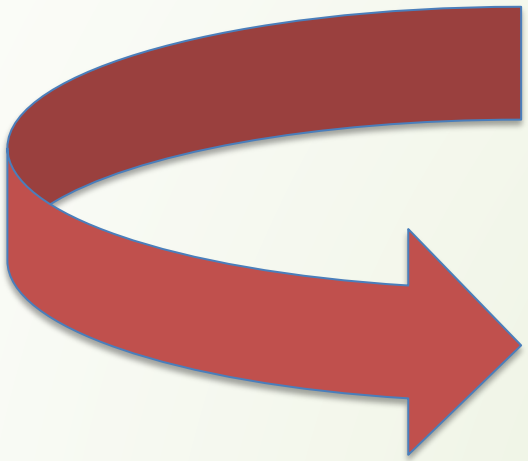
Translocations: Pairing At Meiosis 1

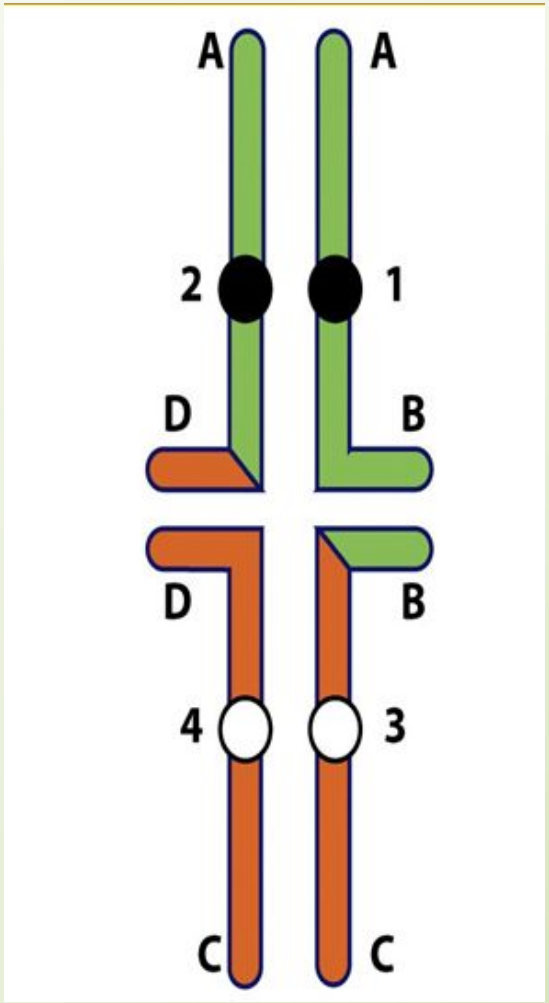
- Translocations have pieces of two different chromosomes attached together, Hence
  - they pair up in a **cross-like/cruciform configuration.**

Cruciform Structure

- Three-dimensional, not flat,
- There is ambiguity about which centromeres are attached to which pole of the spindle. And how segregation will occur?


A
1
B
A
2
D
Normal chromosomes
Translocated chromosomes
C
3
B
C
4
D




A
A
2
1
D
B
D
B
4
3
C
C

segregation at Anaphase

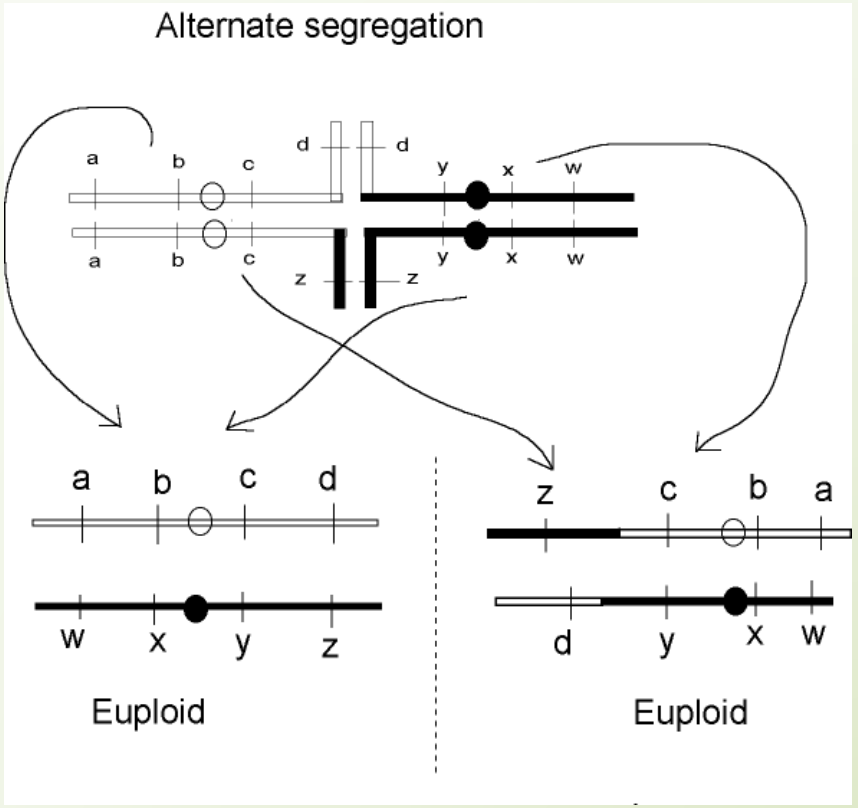
Alternate segregation, where centromeres on opposite sides of the cross go to the same pole

Adjacent segregation (I and II), where centromeres on the same side of the cross go to the same pole

Alternate Segregation

centromeres on opposite sides of the cross go to the same pole in anaphase

- It results in euploid gametes
- 50% of gametes get both of the normal chromosomes
- 50% of the gametes get both of the translocation chromosomes.



Adjacent Segregation I and II

- centromeres on the same side of the cross go to the same pole
- Adjacent segregation results in aneuploid gametes (which die)
- each gamete gets one normal chromosome and one translocation chromosome,
- Hence, some genes are duplicated and some deleted in each gamete.

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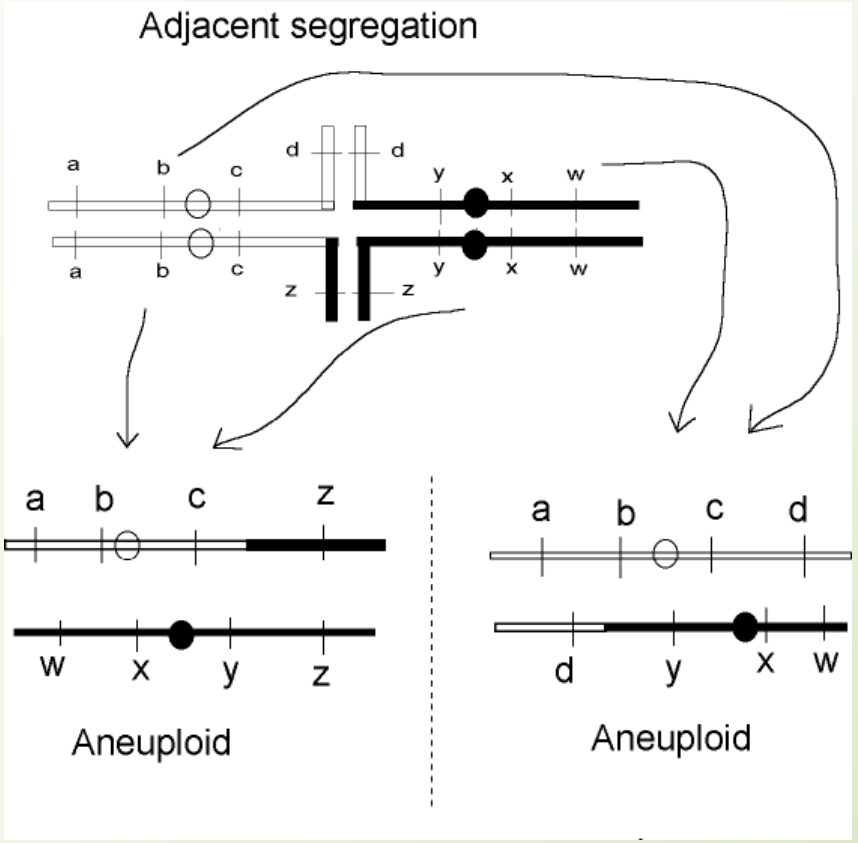

Translocation heterozygote

- Alternate and adjacent segregation occur with about equal frequency, so in a translocation heterozygote about **half the gametes are euploid and viable,** and the other **half are aneuploid and result in a dead embryo**

- This condition with 50% progeny of parents heterozygous for a reciprocal translocation surving is called **semisterility** It results in partial monosomy or trisomy, leading to a variety of birth defects.

Compound chromosome

- One chromosome can fuse with its homologue or two sister chromatids can become attached to one another forming a single genetic unit.
- Can exist stably till division
- It can also be formed by union of two segments of homologous chromosomes.

A

(a) A normal pair of homologous chromosomes (each has one blue arm and one green arm).

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(b) A pair of compound chromosomes (one has two blue arms, the other has two green arms).

Compound chromosome

- In Drosophila right arms of chromosome number two may detach from their left arms and fuse at centromere. This is called **ISOCHROMOSOME** (As two arms are equivalent).

- Compound chromosome therefore differ from translocations as these involve homologous chromosome segments

Compound chromosome

- First discovered in Drosophila 1922 by Lilian morgan
- Formed by union of two X chromosome (double-X/attached X chromosome)
- These flies produce two types of eggs: diplo-X or nullo-X