Variation in Chromosome structure and number

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Types of Chromosomal Mutations

1. Variations in chromosome structure or number can arise spontaneously or be induced by chemicals or radiation.

2. Chromosomal aberrations contribute significantly to human miscarriages, stillbirths and genetic disorders.
   a. About 1⁄2 of spontaneous abortions result from major chromosomal mutations.
   b. Visible chromosomal mutations occur in about 6/1,000 live births.
   c. About 11% of men with fertility problems, and 6% of those institutionalized with mental deficiencies have chromosomal mutations.

Variations in Chromosome Structure

Mutations involving changes in chromosome structure occur in four common types:

a. Deletions.

b. Duplications.

c. Inversions (changing orientation of a DNA segment).

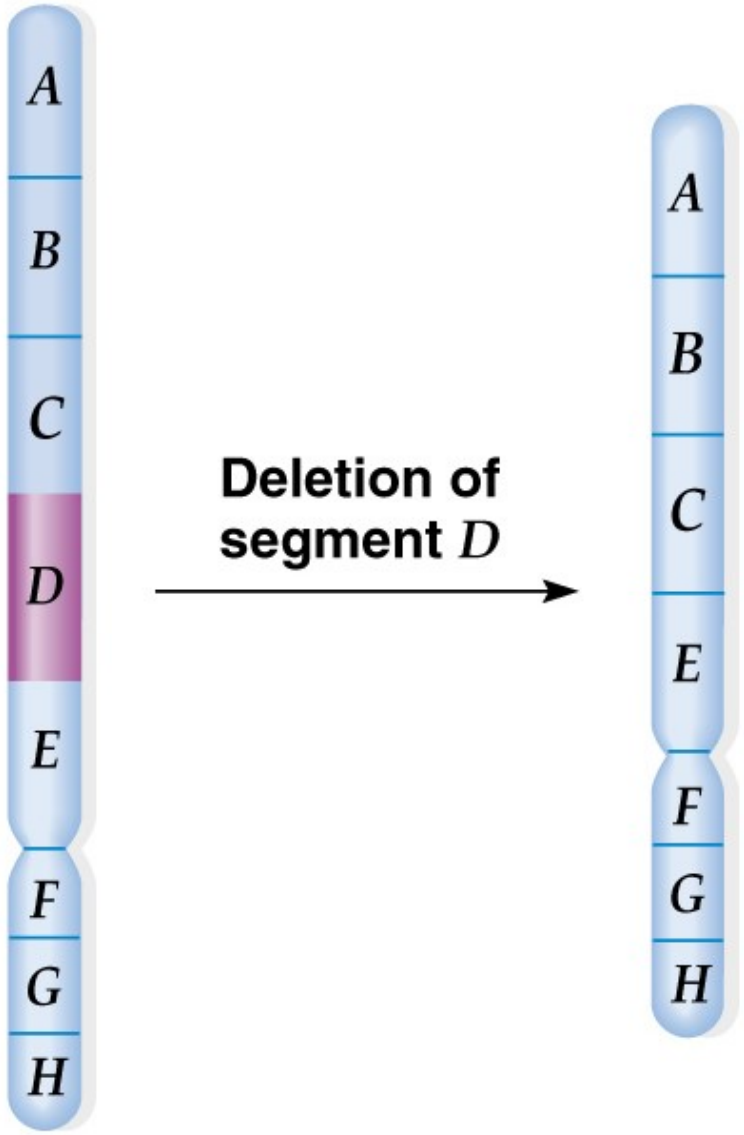
d. Translocations (moving a DNA segment).

Deletion

1. In a deletion, part of a chromosome is missing.
    a. Deletions start with chromosomal breaks induced by:
        i. Heat or radiation (especially ionizing).
        ii. Viruses.
        iii. Chemicals.
        iv.Transposable elements.
        v. Errors in recombination.
    b. Deletions do not revert, because the DNA is missing.

2. The effect of a deletion depends on what was deleted.
    a. 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.
    b. 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.)

Fig. 17.2 A deletion of a chromosome segment



Duplication

1. Duplications result from doubling of chromosomal segments, and occur in a range of sizes and locations
    a. Tandem duplications are adjacent to each other.
    b. Reverse tandem duplications result in genes arranged in the opposite order of the original.
    c. Tandem duplication at the end of a chromosome is a terminal tandem duplication
    d. Heterozygous duplications result in unpaired loops, and may be detected cytologically.

Fig. 17.5 Duplication, with a chromosome segment repeated

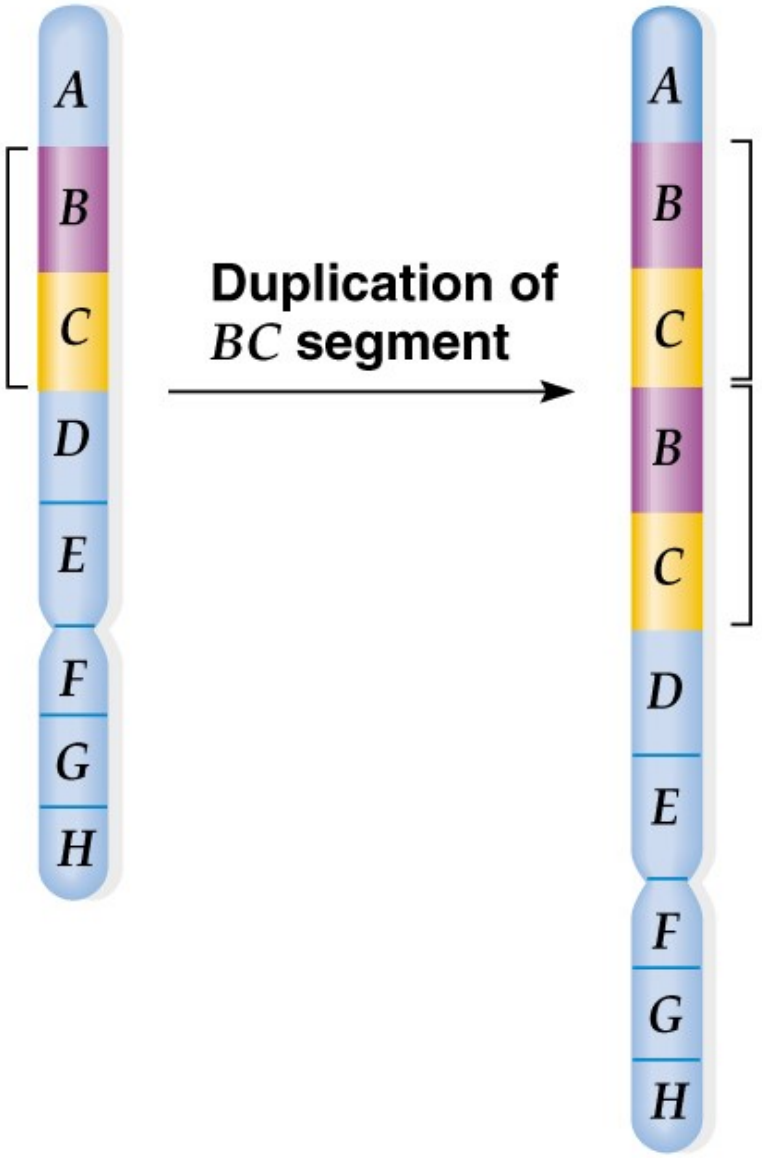


Fig. 17.6 Forms of chromosome duplications are tandem, reverse tandem, and terminal tandem duplications

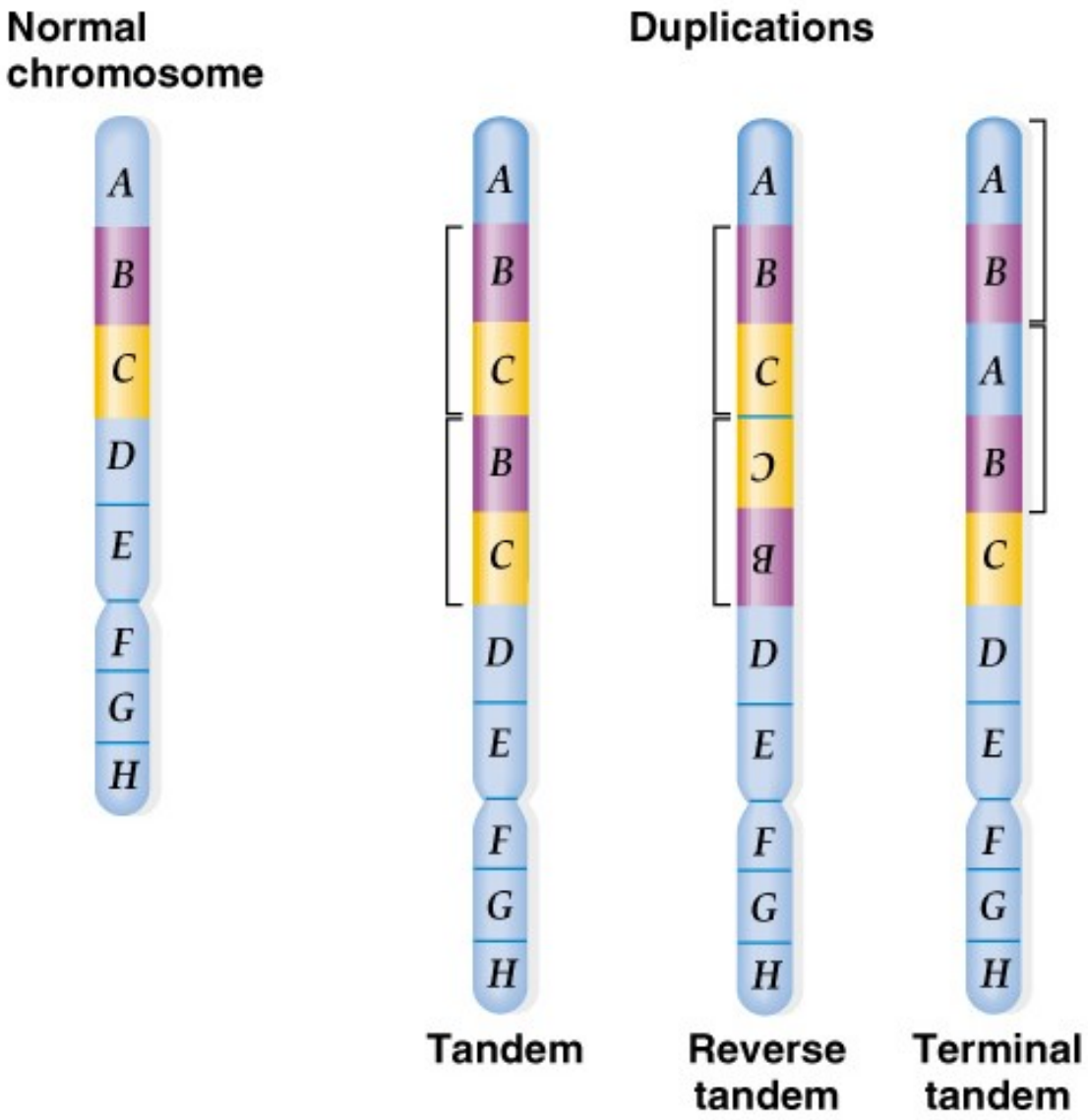
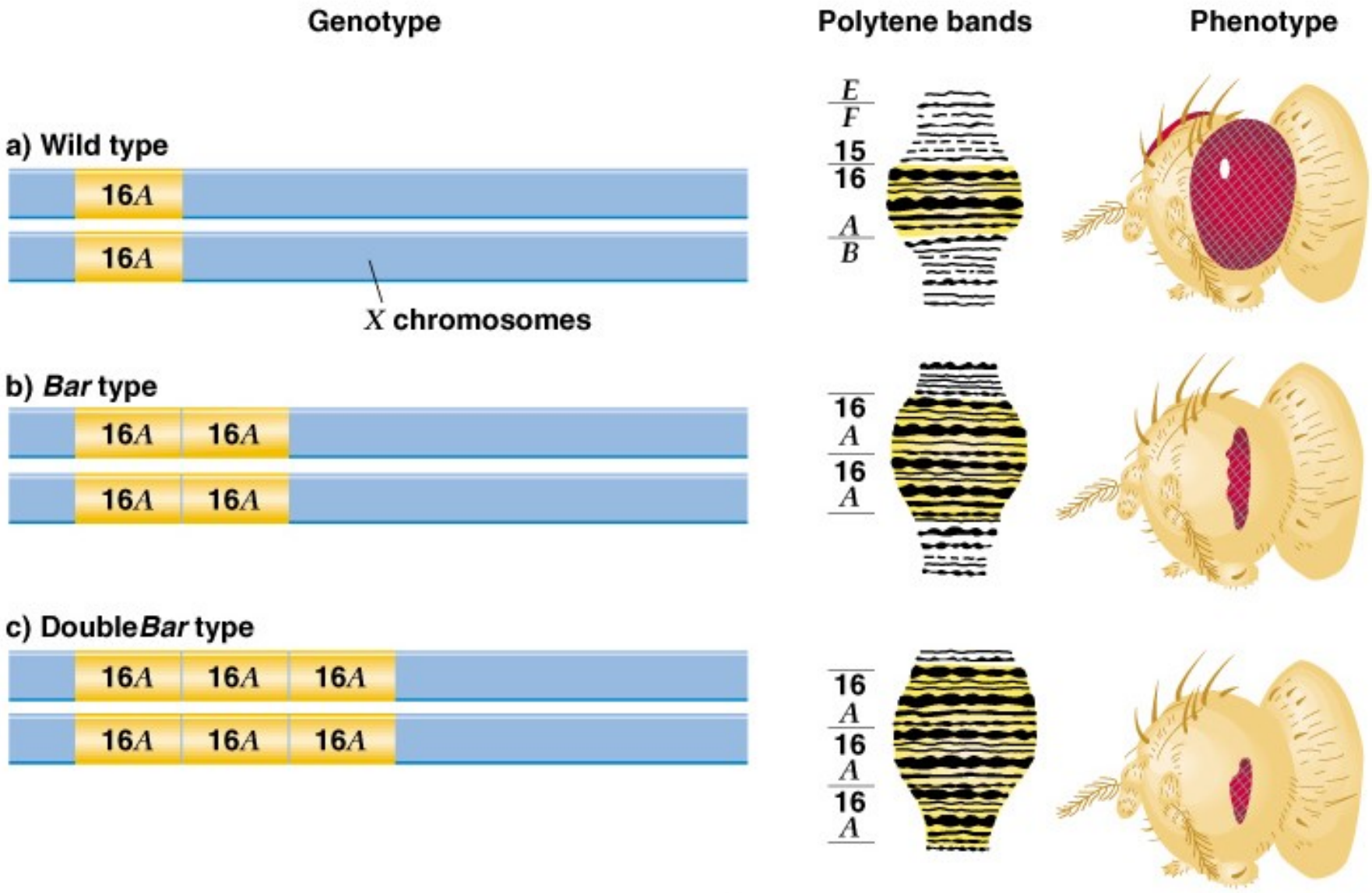


Fig. 17.7 Chromosome constitutions of *Drosophila* strains



Inversion

1. Inversion results when a chromosome segment excises and reintegrates oriented 180° from the original orientation. There are two types (Figure 17.8):

   a. Pericentric inversions include the centromere.

   b. Paracentric inversions do not include the centromere.

2. Inversions generally do not result in lost DNA, but phenotypes can arise if the breakpoints are in genes or regulatory regions.

Fig. 17.8 Inversions

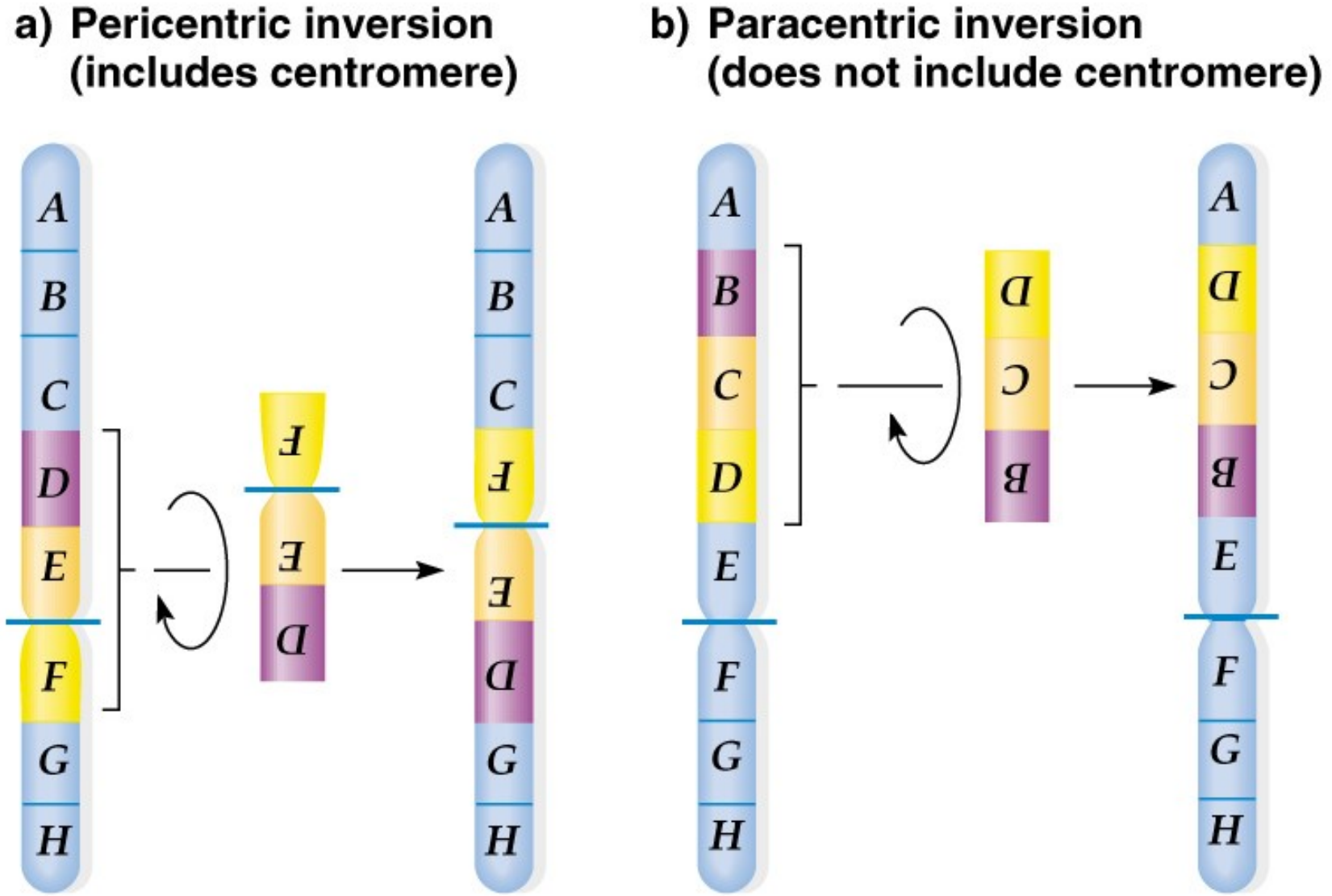
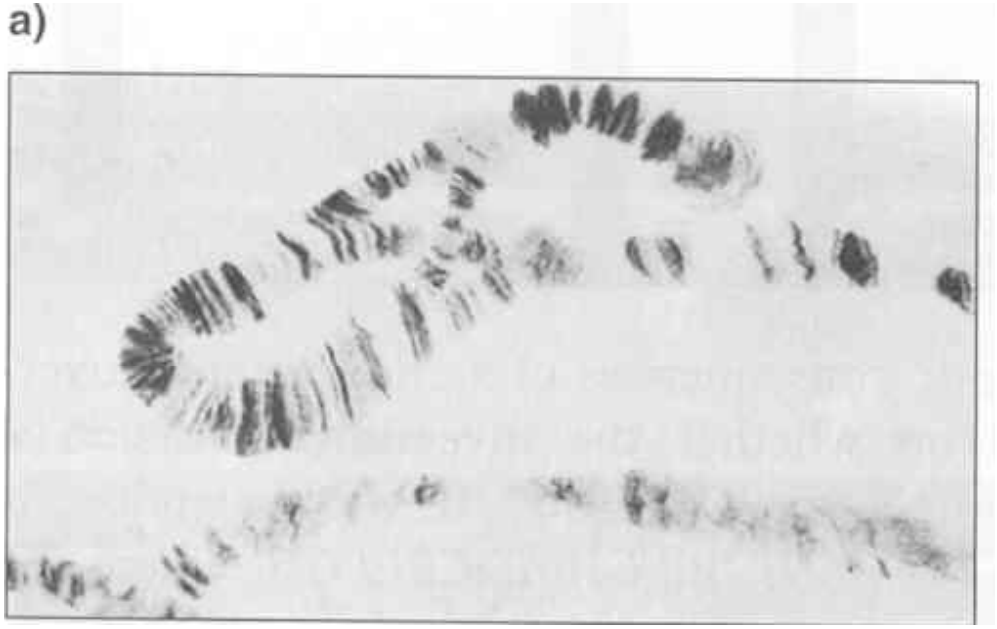


Fig. 17.9 Consequences of crossing-over in a paracentric inversion



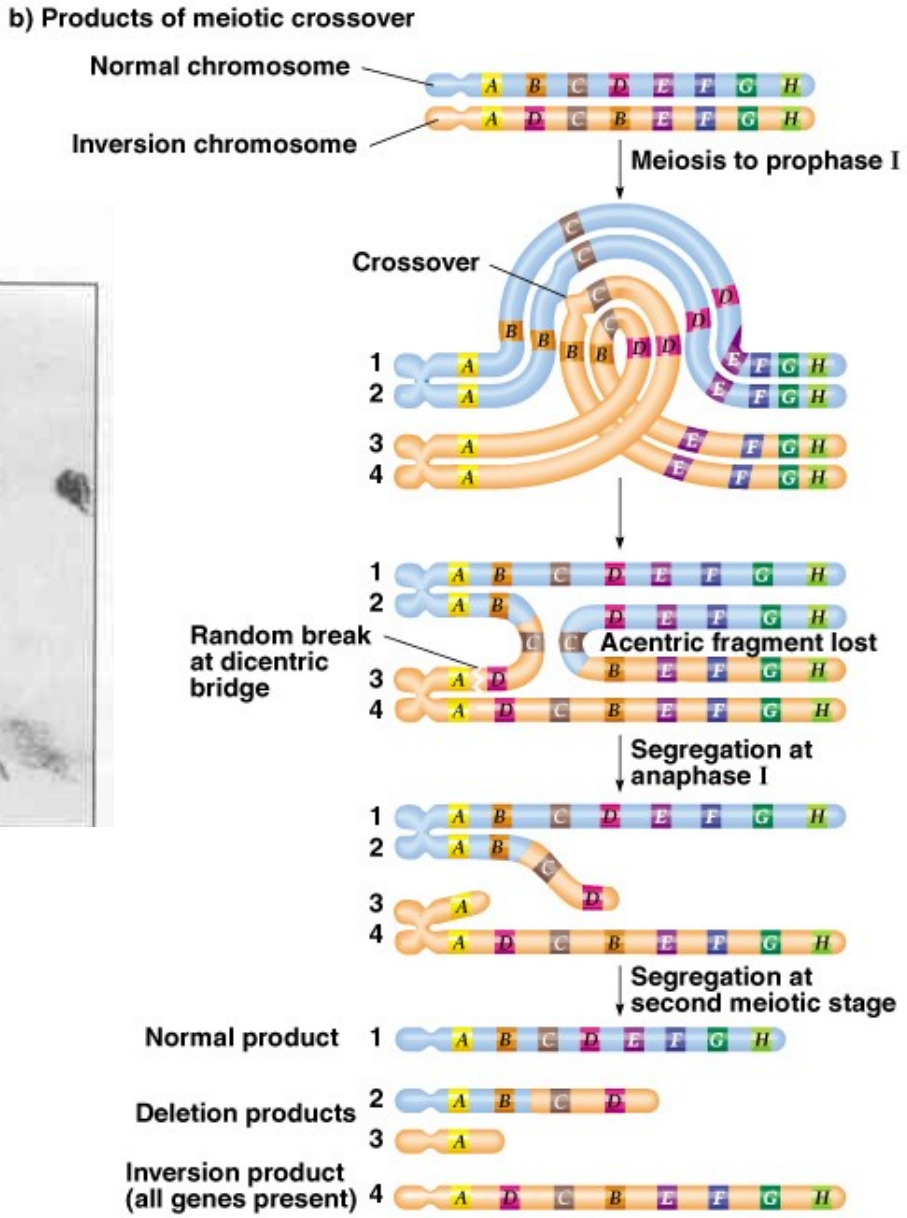
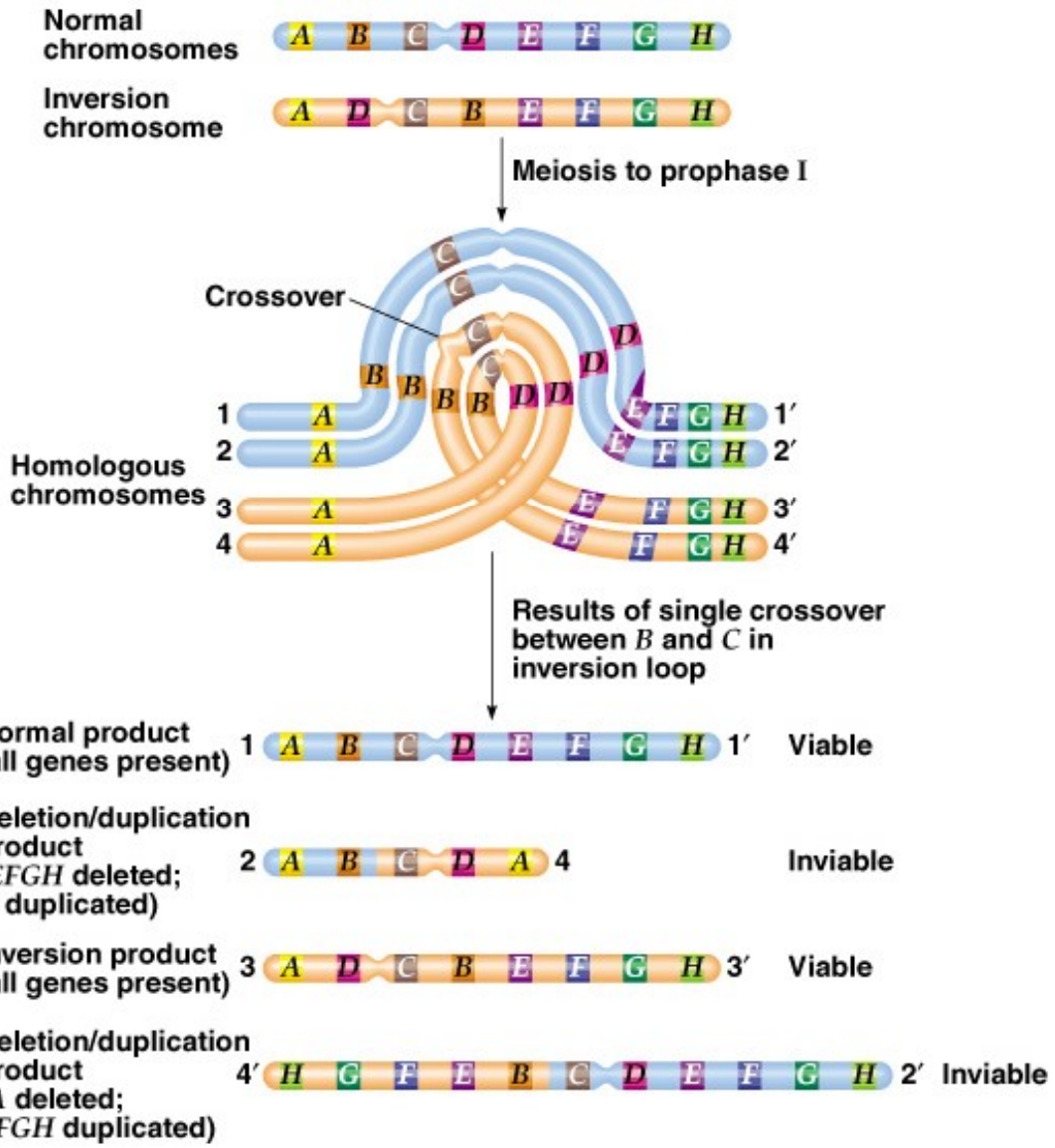


Fig. 17.10 Meiotic products resulting from a single crossover within a heterozygous, pericentric inversion loop



Translocation

1. A change in location of a chromosome segment is a translocation. No DNA is lost or gained. Simple translocations are of two types:
    a. Intrachromosomal, with a change of position within the same chromosome.
    b. Interchromosomal, with transfer of the segment to a nonhomologous chromosome.
        i. If a segment is transferred from one chromosome to another, it is nonreciprocal.
        ii. If segments are exchanged, it is reciprocal.

Fig. 17.11 Translocations

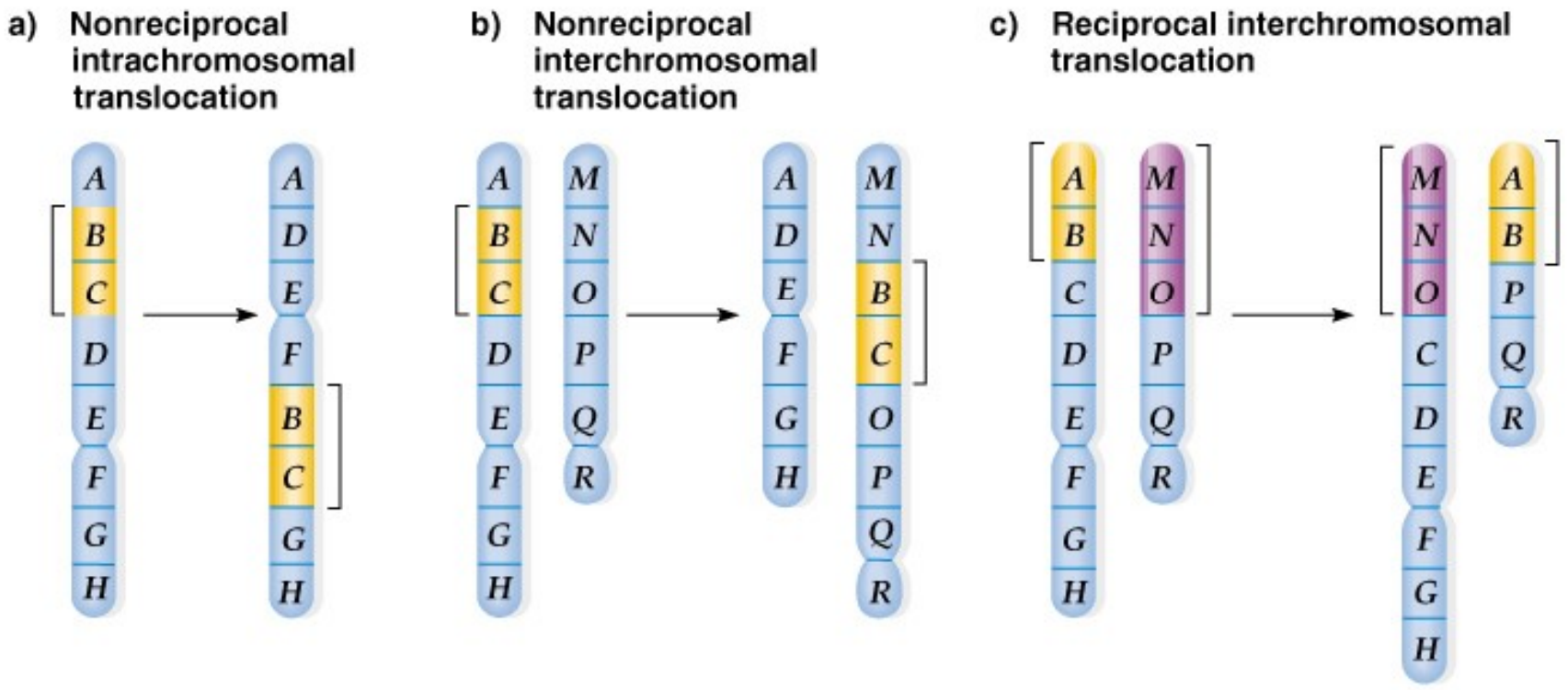
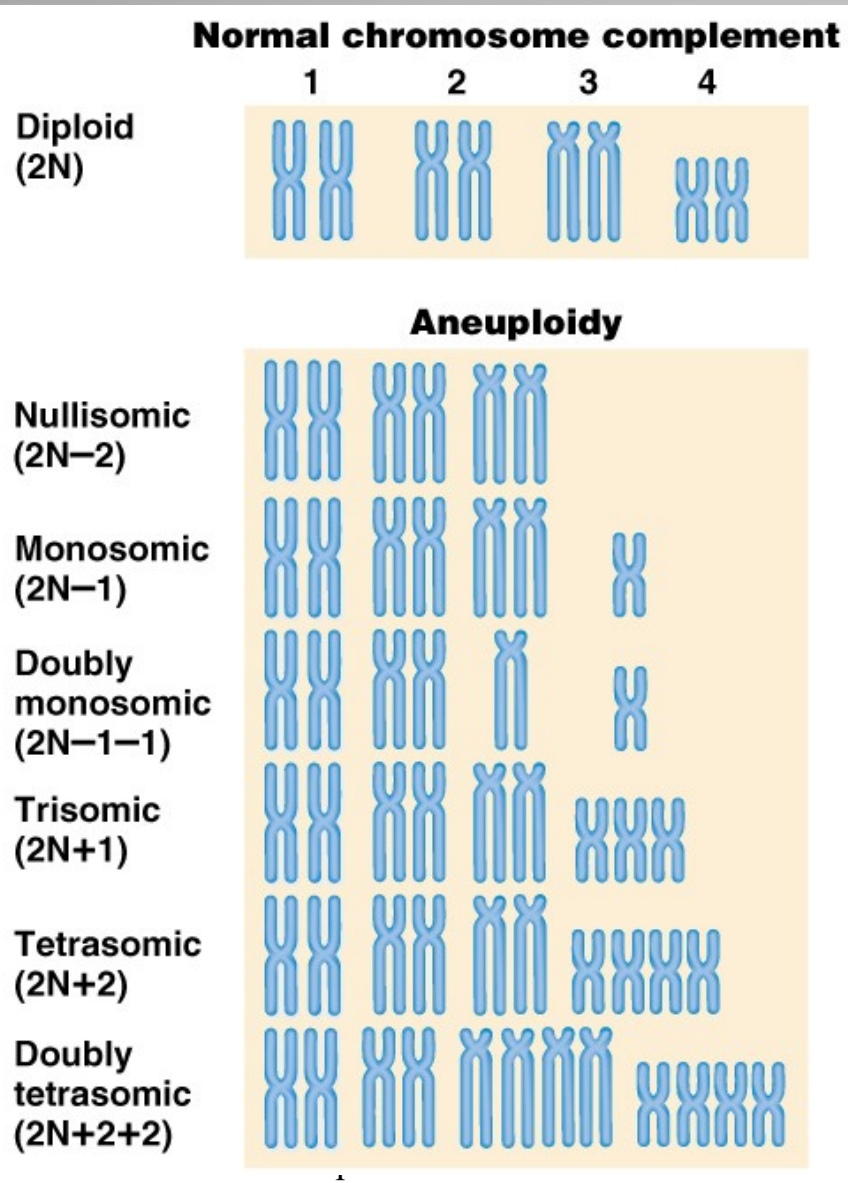


Fig. 17.16 Normal (theoretical) set of metaphase chromosomes in a diploid (2N) organism *(top)* and examples of aneuploidy *(bottom)*



Introduction

- Teratology

- Causes of congenital malformations:
  (a) Genetic factors: chromosomal abnormalities
  (b) Environmental factors: drugs, viruses

- Types of chromosomal abnormalities:
  (a) Numerical
  (b) Structural

Numerical Chromosomal Abnormalities

- Changes in the number of chromosomes:
  - Polyploidy
    - Somatic cells contain multiples of haploid number of chromosomes
    - 3n, 4n, 5n etc.
  - Aneuploidy (Heteroploidy)
    - Deviation from the diploid number of chromosomes
    - 2n + 1, 2n -1 etc.

Mechanism of Polyploidy

(a) Failure of pulling apart of 2 chromatids to opposite ends after metaphase stage of mitosis.

(b) Reduplication of chromosomes without dissolving of nuclear membrane.

(c) Failure of cytoplasmic division.

Types of Polyploidy

1. Autopolyploidy: even-numbered multiples of haploid number of chromosomes. e.g.-

   (a) Tetraploidy (23x4 or 92 chromosomes)

   (b) Hexaploidy (23x6 or 138 chromosomes)

   (c) Octaploidy (23x8 or 184 chromosomes)

   etc.

Types of Polyploidy

2. Allopolyploidy: odd-numbered multiples of haploid number of chromosomes. e.g.-

(a) Triploidy (23x3 or 69 chromosomes)-commonest

(b) Pentaploidy (23x5 or 115 chromosomes)

(c) Heptaploidy (23x7 or 161 chromosomes)

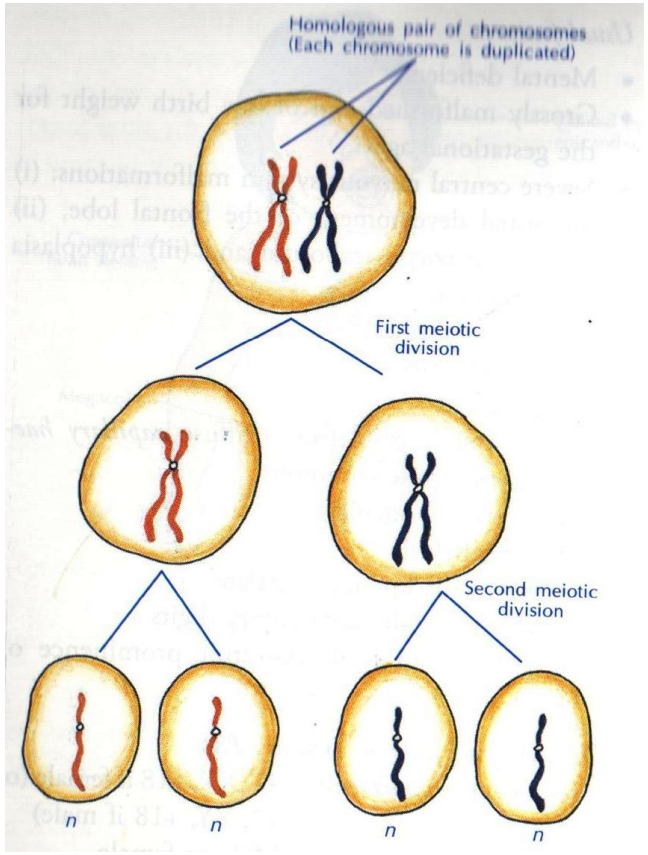
etc.

Mechanism of Aneuploidy

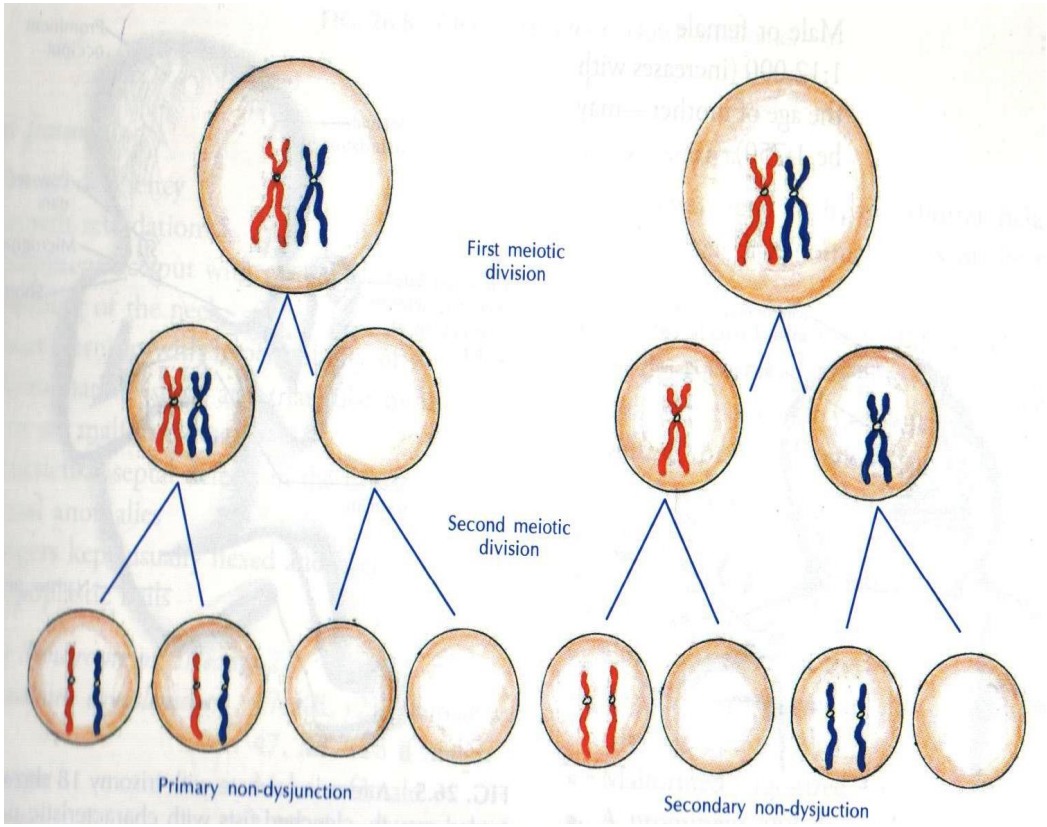
Non-dysjunction: failure of separation of chromosomes during cell division.

- Formation of 2 types of gametes (both abnormal)
- Fusion of either of these abnormal gametes with a normal gamete can result in trisomy or monosomy
- May involve autosomes or sex chromosomes

Normal 1st & 2nd meiotic division



Two types of non-disjunction



Trisomies of Chromosomes

- Presence of 3 copies of a chromosome
- Trisomy of Autosomes (13,18,21)
- Trisomy of Sex Chromosomes (XXX, XXY)

Trisomy of Autosomes

- Trisomy 13 or D-trisomy (Patau syndrome)
- Trisomy 18 or E-trisomy (Edward syndrome)
- Trisomy 21 or G-trisomy (Down syndrome)

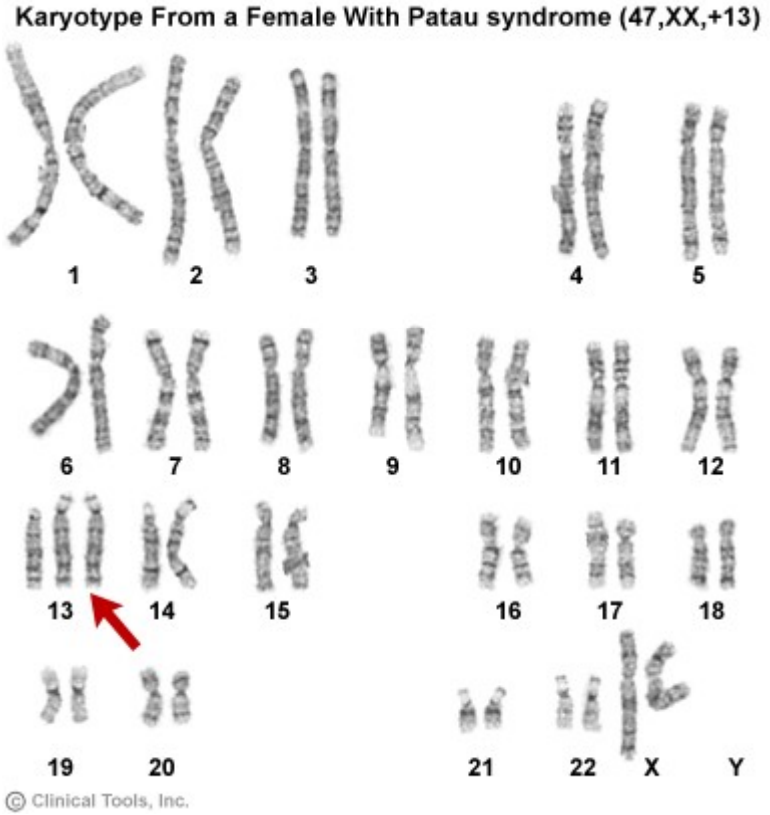
Trisomy 13 (Patau Syndrome)

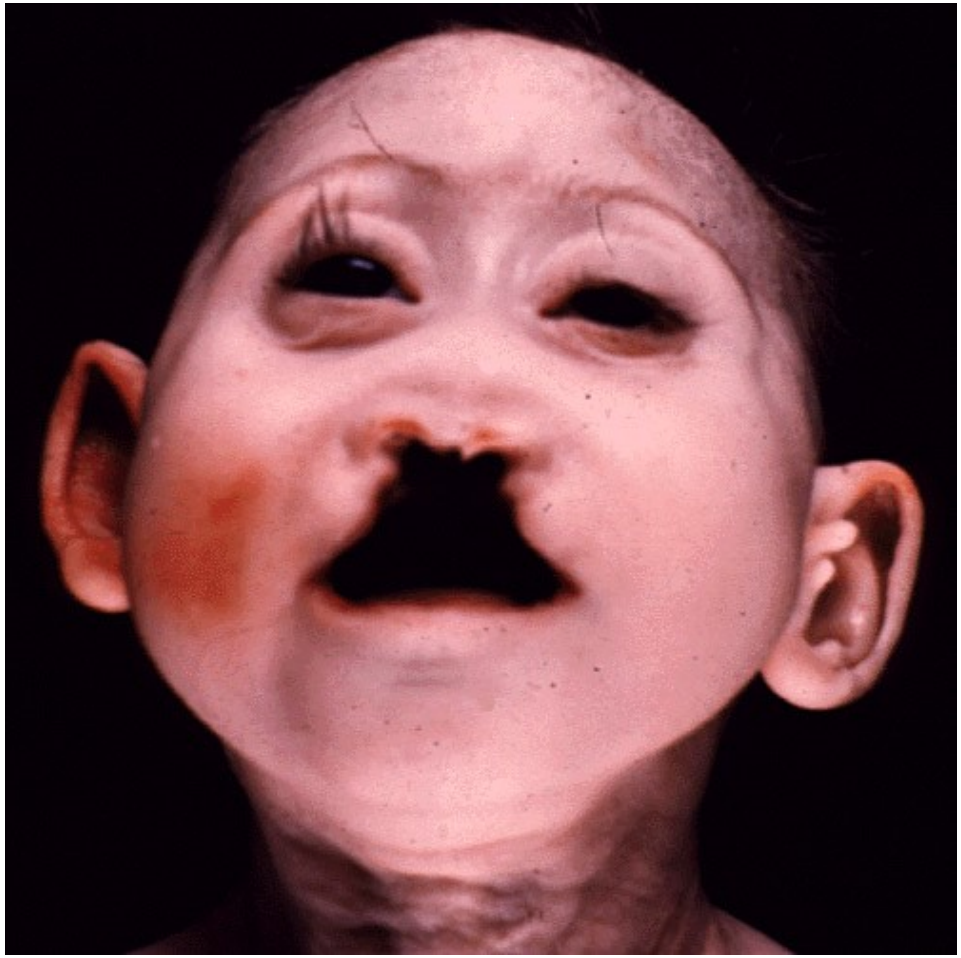
- 1st described by Bartholin (1657) & redefined by Patau (1960).
- Chromosomal complement: 47,XX,+13 (female) or 47,XY,+13 (male)
- Phenotype: Male or female
- Incidence: 1:12,000 (increases with the age of mother)

Features of Patau Syndrome

- Mental deficiency
- Low birth weight
- Abnormal development of frontal lobe
- Absence of corpus callosum
- Hypoplasia of cerebellum
- Sloping forehead
- Scalp defects
- Malformed ears
- Congenital heart defects
- Renal tract anomalies
- Microphthalmia
- Bilateral cleft lip/palate
- Polydactyly with rudimentary digits
- Rocker-bottom heel

Patau syndrome





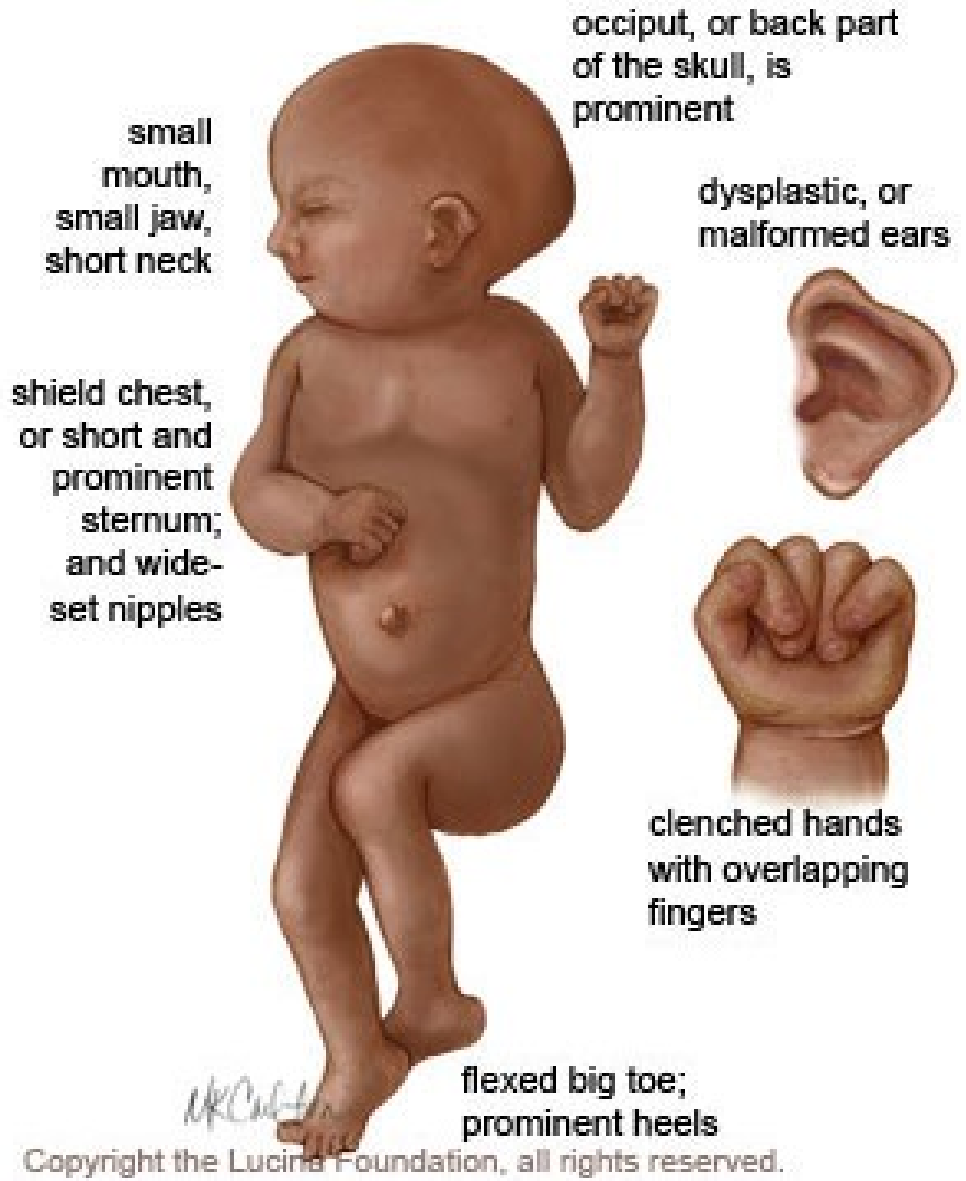
Trisomy 18 (Edward Syndrome)

- Chromosomal complement: 47,XX,+18 (female) or 47,XY,+18 (male)
- Phenotype: Male or female
- Incidence: 1:8000

Features of Edward Syndrome

- Mental deficiency
- Growth retardation
- Prominent occiput with elongated head
- Webbing of the neck
- Short sternum
- Micrognathia
- Low-set malformed ears
- Ventricular septal defects
- Renal anomalies
- Clenched fists with overlapping of fingers
- Hypoplastic nails

Edward syndrome



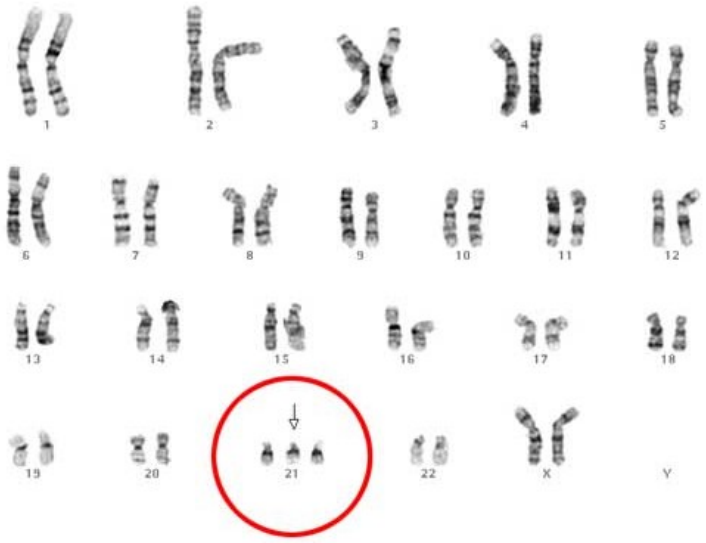
Trisomy 21 (Down Syndrome)

- Chromosomal complement: 47,XX,+21 (female) or 47,XY,+21 (male)
- Phenotype: Male or female
- Incidence: 1:800 (increases with the age of mother)

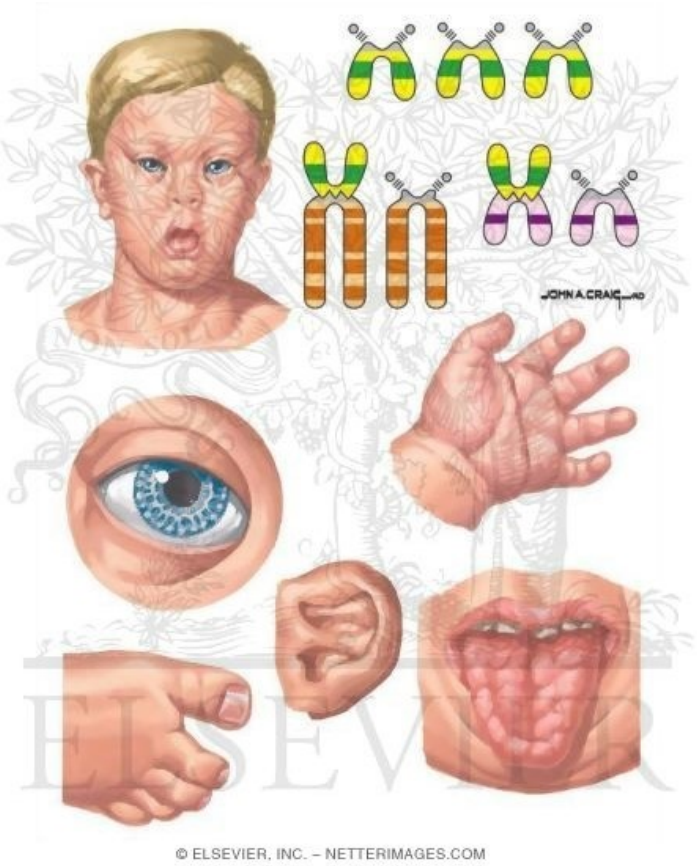
Features of Down Syndrome

- Short height
- Severe mental deficiency with decline in the IQ with age
- Brachycephaly with flat face and occiput
- Flat and low nasal bridge
- Upward slant to palpebral fissures
- Malformed large ears
- Epicanthal folds of the eyes
- Brushfield spots in iris
- Renal anomalies
- Prominent and protruding tongue (scrotal tongue)
- Simian crease
- Clinodactyly of 5th digit

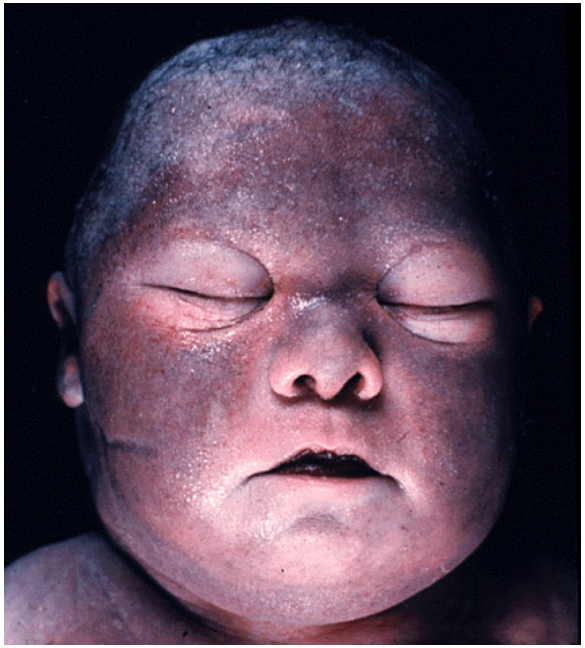
Down Syndrome

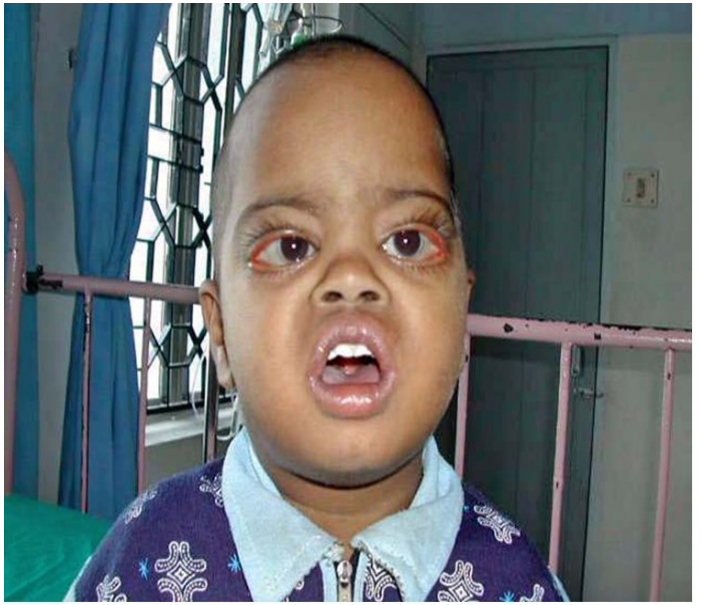


Down syndrome



Down syndrome





Syllabus
Fundamentals of Genetics AGP-111

Pre and Post Mendelian concepts of heredity, Mendelian principles of heredity. Architecture of chromosome; chromonemata, chromosome matrix, chromomeres, centromere, secondary constriction and telomere; special types of chromosomes. Chromosomal theory of inheritance- cell cycle and cell division- mitosis and meiosis. Probability and Chi-square. Dominance relationships, Epistatic interactions with example. Multiple alleles, pleiotropism and pseudoalleles, Sex determination and sex linkage, sex limited and sex influenced traits, Blood group genetics, Linkage and its estimation, crossing over mechanisms, chromosome mapping. Structural and numerical variations in chromosome, Use of haploids, dihaploids and doubled haploids in Genetics. Mutation, classification, Methods of inducing mutations & CIB technique, mutagenic agents and induction of mutation. Qualitative & Quantitative traits, Polygenes and continuous variations, multiple factor hypothesis, Cytoplasmic inheritance. Genetic disorders. Nature, structure & replication of genetic material. Protein synthesis, Lac operon.