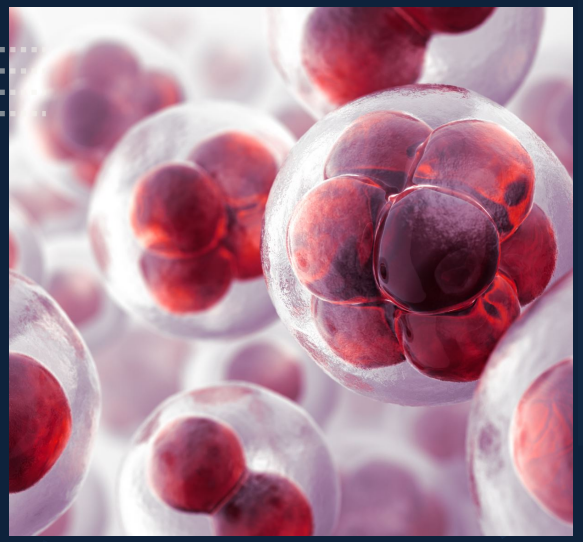
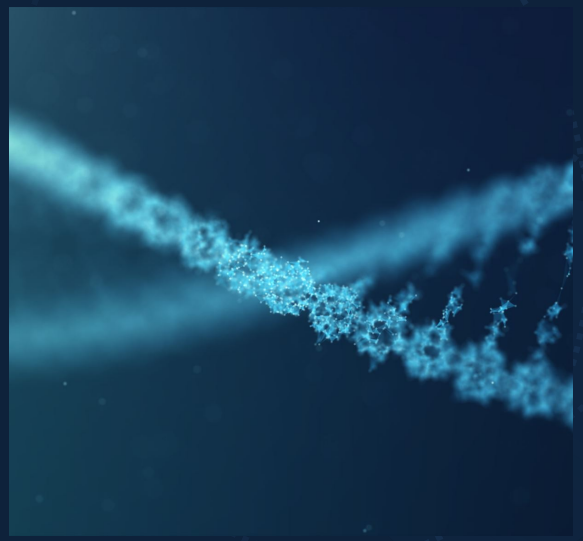
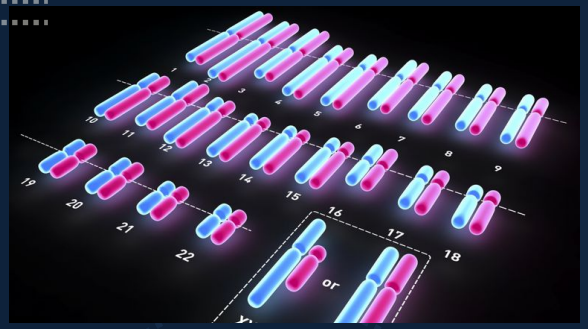
Chromosomal abberations

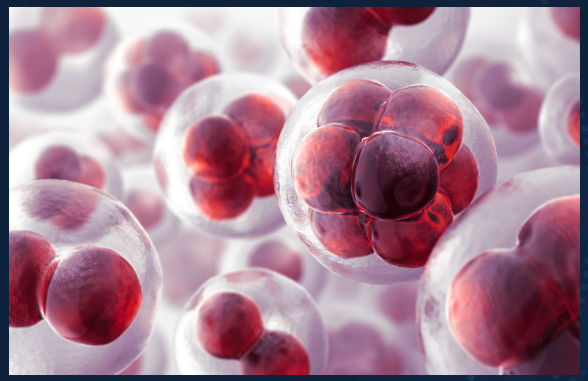




Numerical abberations

Variation in chromosomal numbers: Aneuploidy





Numerical. Abberations are of two basic types:

1. Changes in *whole* chromosome sets, resulting in a condition called ***aberrant euploidy***

2. Changes in *parts* of chromosome sets, resulting in a condition called ***aneuploidy***.

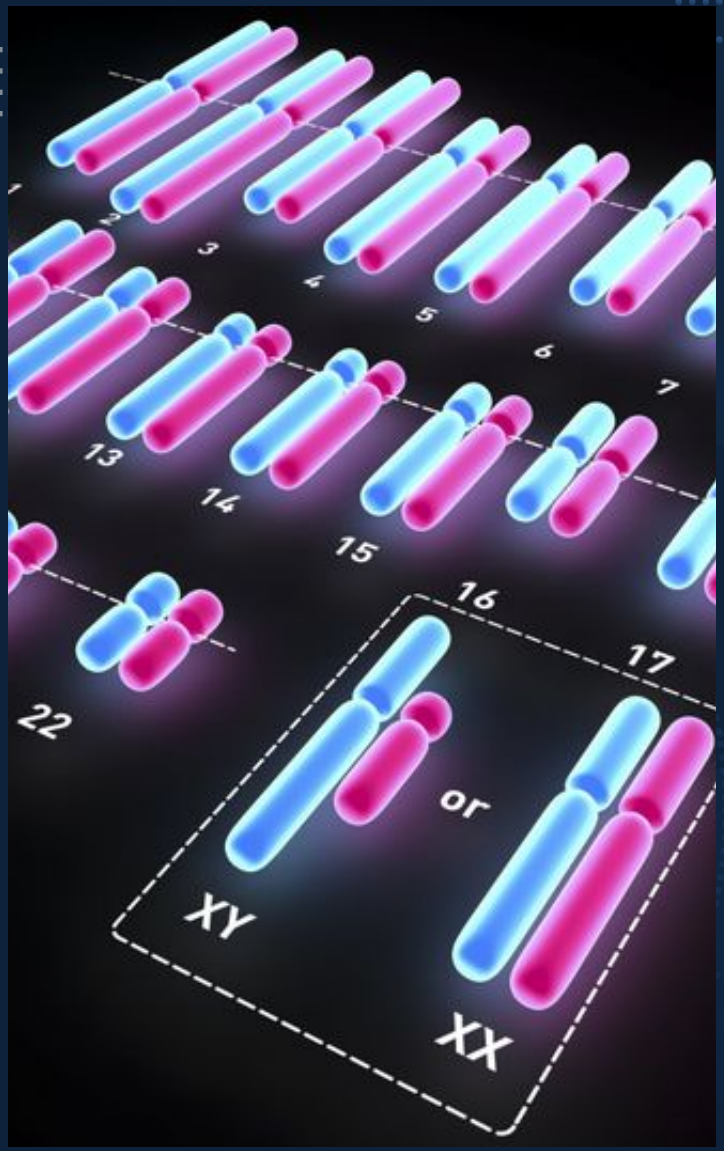
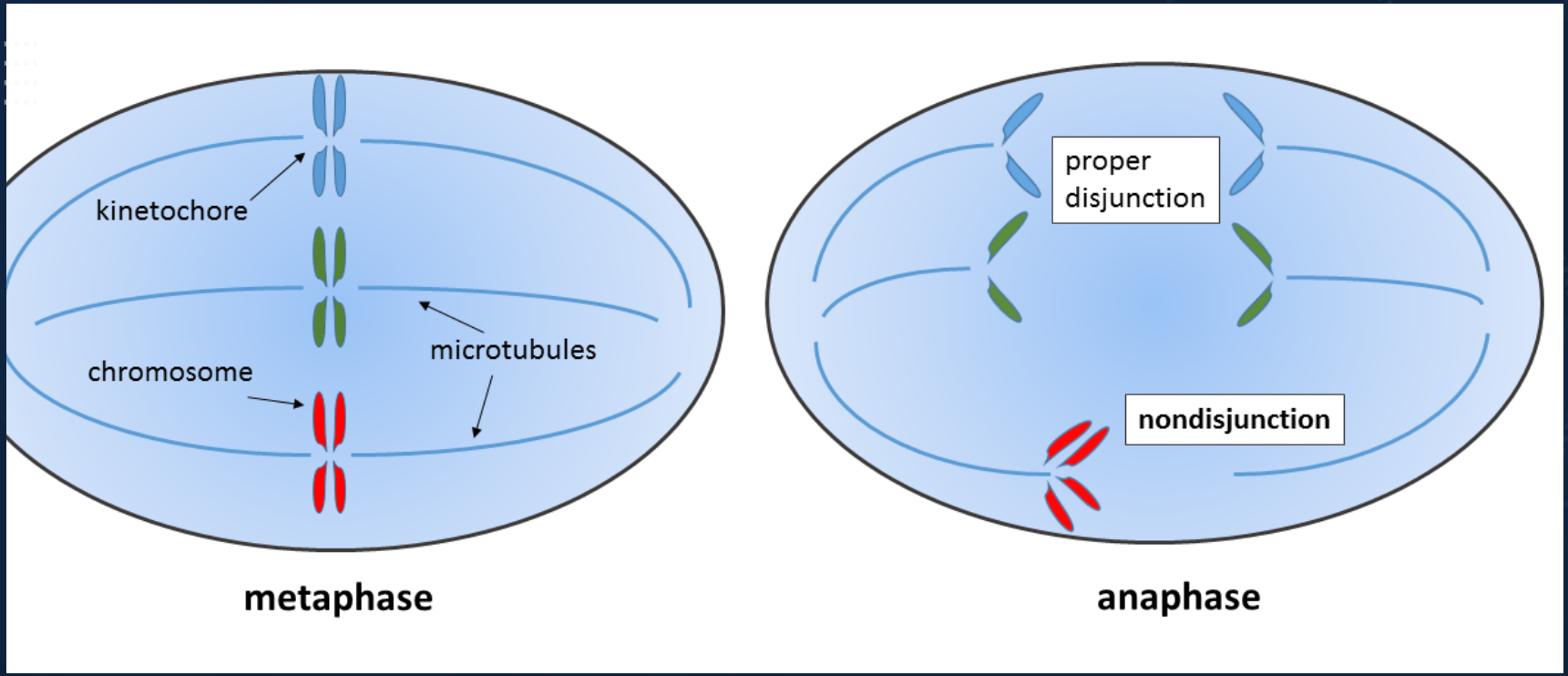


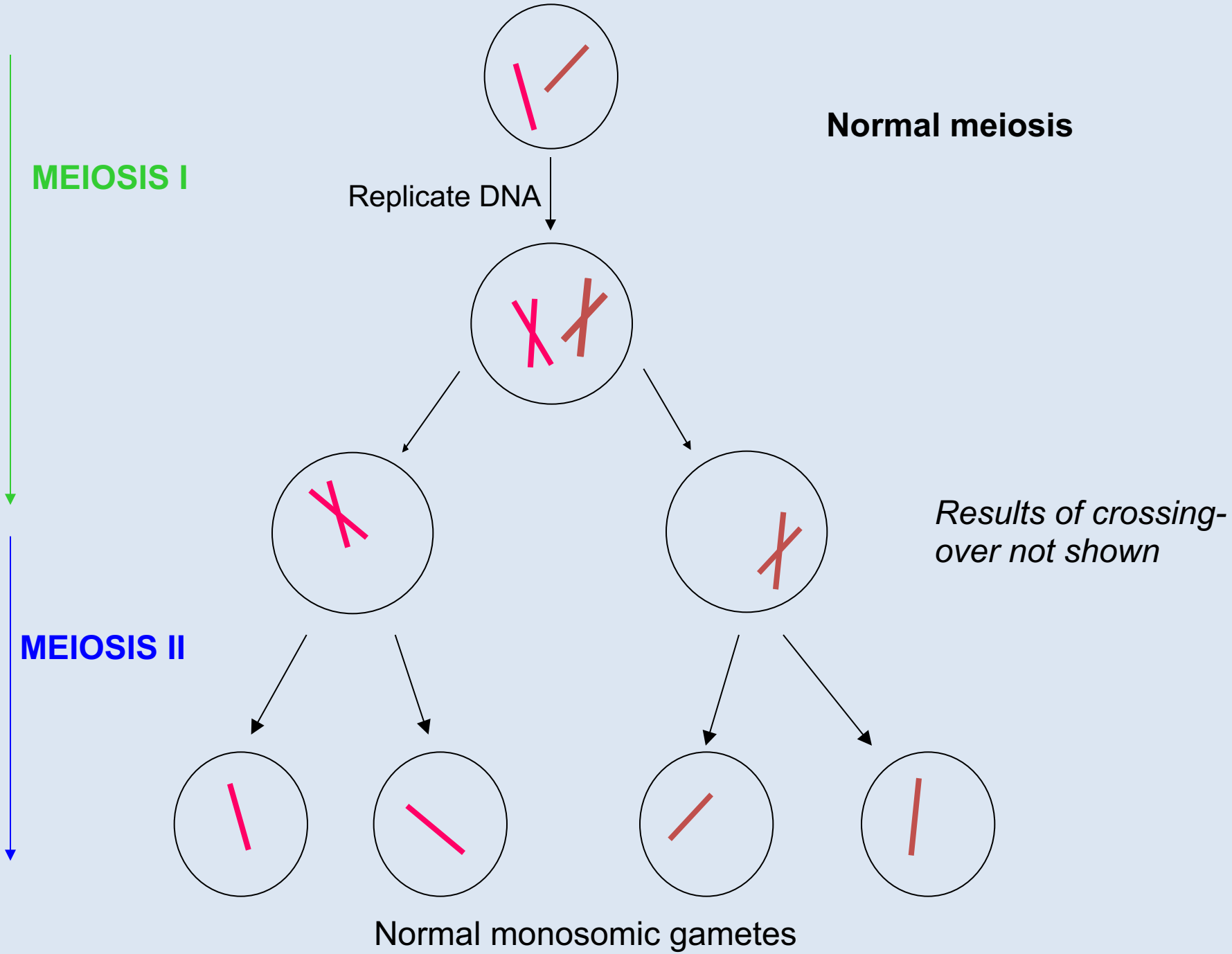
TABLE 15-1 Chromosome Constitutions in a Normally Diploid Organism with Three Chromosomes (Labeled A, B, and C) in the Basic Set

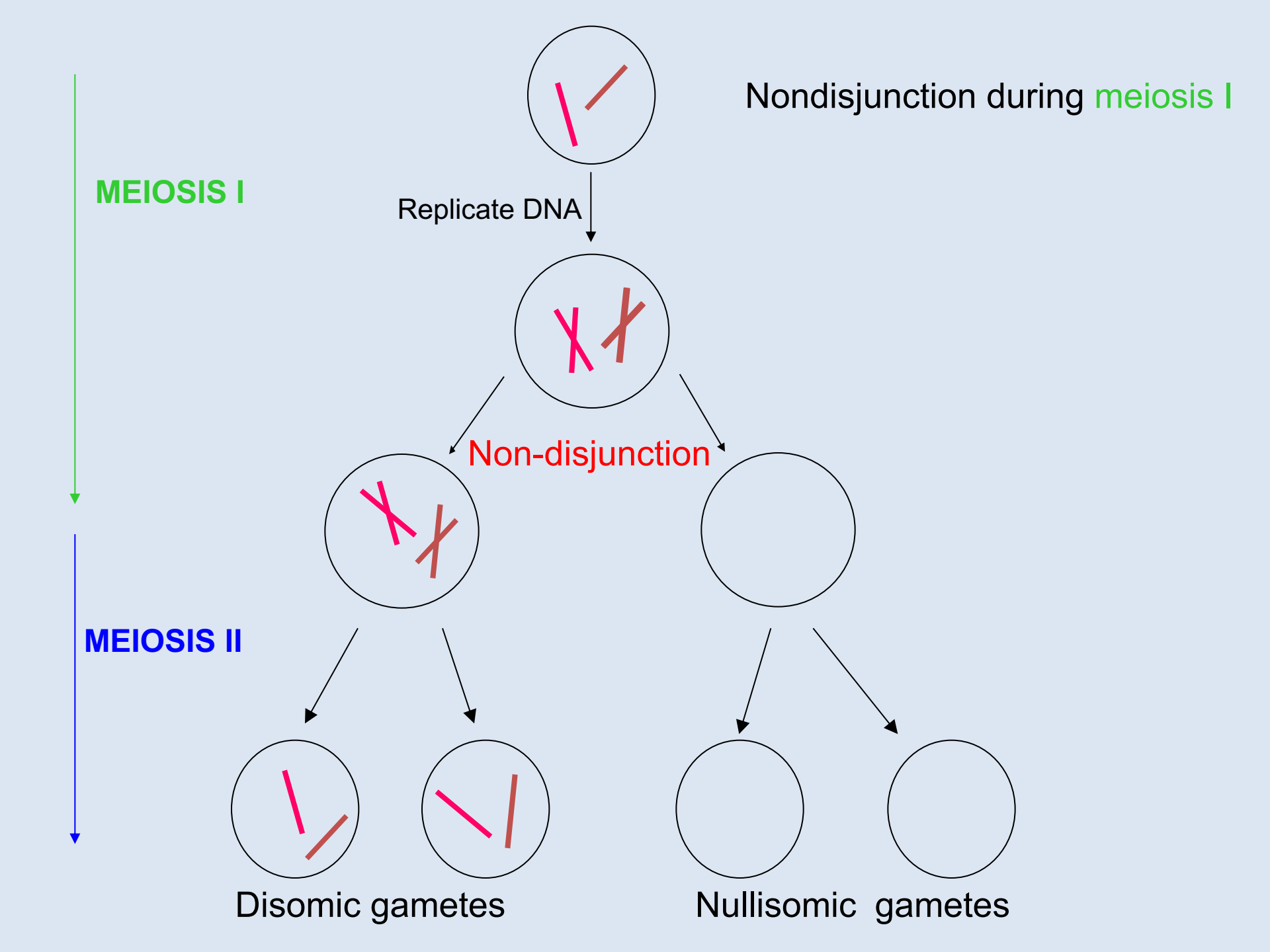
Name	Designation	Constitution	Number of chromosomes
Euploids			
Monoploid	n	A B C	3
Diploid	$2n$	AA BB CC	6
Triploid	$3n$	AAA BBB CCC	9
Tetraploid	$4n$	AAAA BBBB CCCC	12
Aneuploids			
Monosomic	$2n - 1$	A BB CC	5
		AA B CC	5
		AA BB C	5
Trisomic	$2n + 1$	AAA BB CC	7
		AA BBB CC	7
		AA BB CCC	7

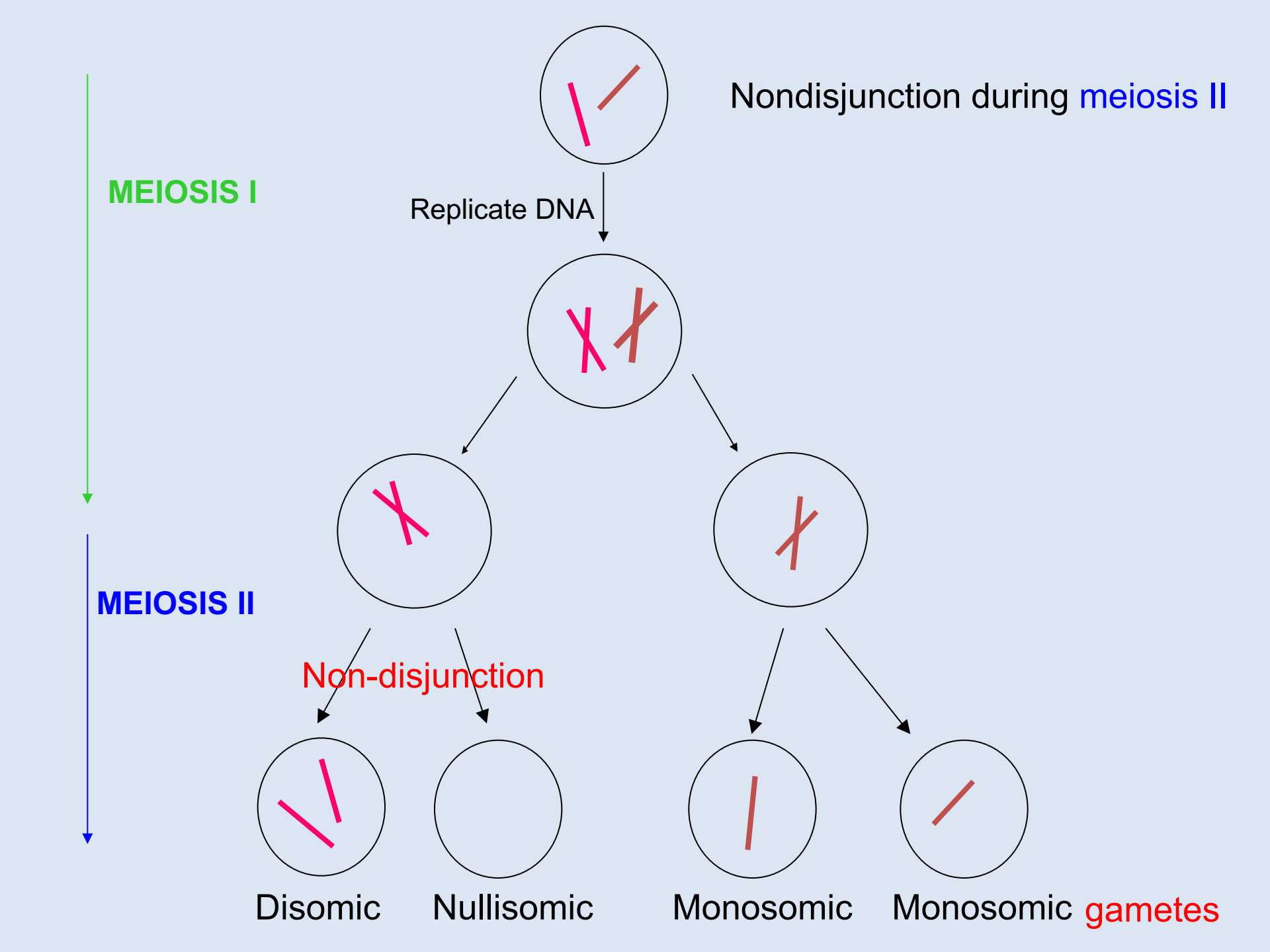
Cause of Aneuploidy: Nondisjunction

- **Nondisjunction** – failure of chromosomes to separate and segregate into daughter cells
  - Nondisjunction may occur during meiosis 1 or meiosis 2
  - Abnormal number of chromosomes may result




Normal meiosis
MEIOSIS I
Replicate DNA
Results of crossing-over not shown
MEIOSIS II
Normal monosomic gametes


Nondisjunction during meiosis I
MEIOSIS I
Replicate DNA
Non-disjunction
MEIOSIS II
Disomic gametes
Nullisomic gametes


Nondisjunction during meiosis II
MEIOSIS I
Replicate DNA
MEIOSIS II
Non-disjunction
Disomic
Nullisomic
Monosomic
Monosomic gametes

1. Turner syndrome

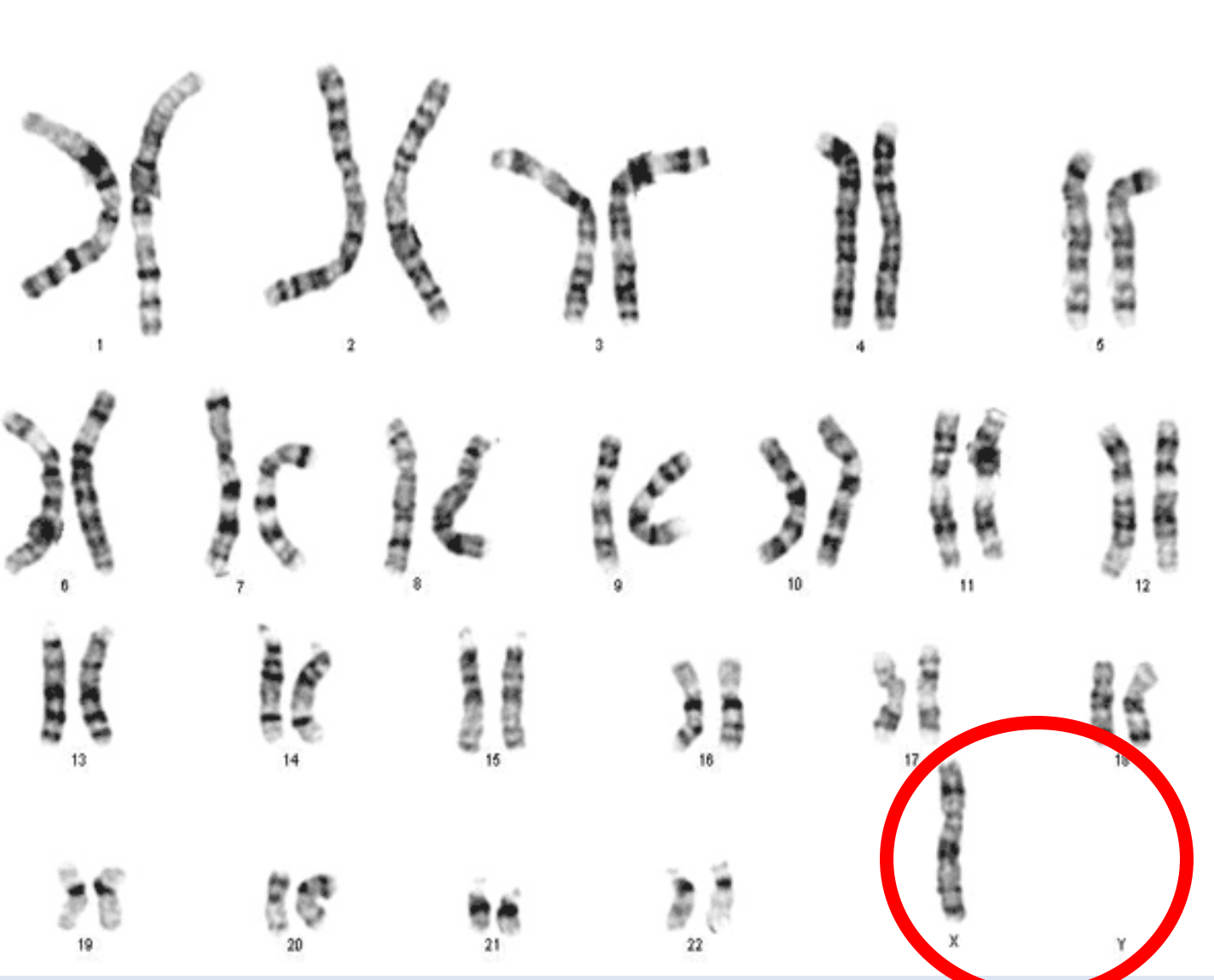
- Also known as "Gonadal Dysgenesis"
- **45, X** The female is born without the second X chromosome
- Has 44 autosomes and a single X chromosome

- Human females, monosomy X (absence of an entire sex chromosome, the Barr body)

STATISTICS

- 98% of Turner Syndrome-afflicted fetuses spontaneously abort, making 10% of all miscarriages
- Occurs in about 1/2,000 live female births
- Multiple blood cells may be required to be tested because some cells may carry X monosomy while others may not

TURNER SYNDROME: KARYOTYPE



Turner syndrome: named after Henry Turner the endocrinologist who first described it in 1938

Symptoms

- short stature
- swelling
- broad chest,
- low hairline,
- low-set ears,
- webbed necks.

- gonadal dysfunction (non-working ovaries), which results in amenorrhea (absence of menstrual cycle) and sterility.
- congenital heart disease,
- hypothyroidism (reduced hormone secretion by the thyroid)
- diabetes
- vision problems
- hearing concerns,

Individual may have a combination of symptoms and is unlikely to have all symptoms.

- High waist-to-hip ratio
- Infertility
- Attention Deficit/Hyperactivity Disorder or ADHD (problems with concentration, memory, attention with hyperactivity seen mostly in childhood and adolescence)
- small lower jaw/micrognathia
- Turner syndrome manifests itself differently in each affected female, no two individuals will share the same features.

CAUSE

- Usually caused by non-disjunction
- In majority of cases monosomy X chromosome comes from non-disjunction in mother But may occur due to a nondisjunction in the father.

TURNER SYNDROME

DIAGNOSIS

- Women's amniotic fluid is tested while pregnant.
- If the test is positive, genetic counseling is recommended

TREATMENT/CURE

- certain treatments to help with the symptoms
  - Growth hormone therapy
  - Estrogen/progesterone replacement
  - Close heart monitoring for heart problems

2. Klinefelter's syndrome

- Discovered in1942 by **Dr. Harry Klinefelter** and team at General Hospital in Boston.
- Additional X chromosome,s in males **47,XXY**
- In humans, 47,XXY is the most common sex chromosome aneuploidy in males.
- Occur in 1:500 to 1:1000 live male births

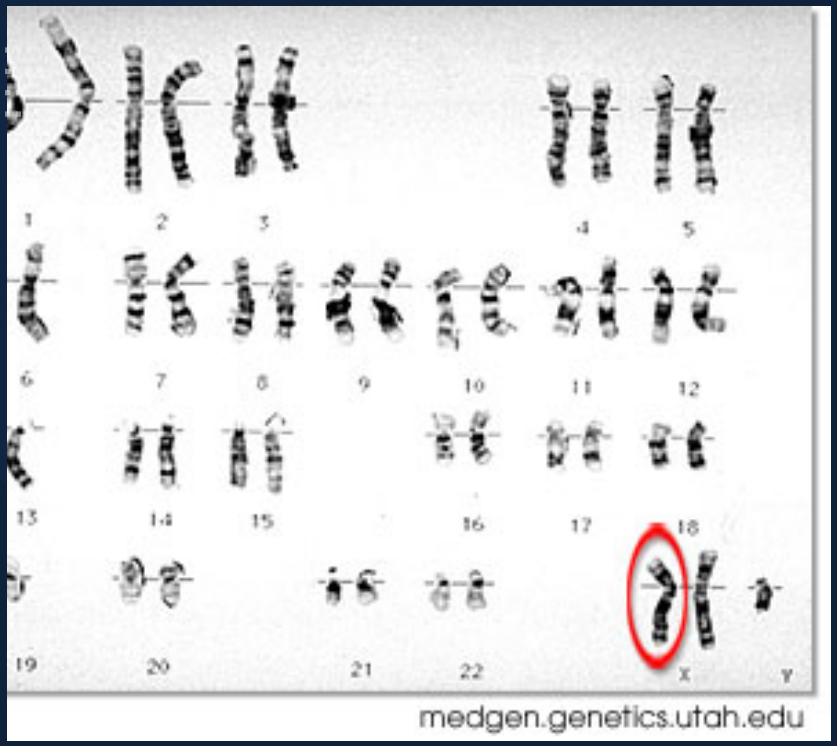
Klinefelter's syndrome

- Cause: nondisjunction event during meiosis I (gametogenesis).
- X and Y sex chromosomes, fail to separate, producing a sperm with both chromosomes X and Y
- Fertilizing a normal (X) egg with this sperm produces an XXY offspring

Klinefelter's Syndrome

- Cause II-nondisjunction event during meiosis II in the female when sister chromatids on the sex chromosome, fail to separate
- An XX egg is produced which, when fertilized with a Y sperm, yields XXY offspring.

Klinefelter's Syndrome



Klinefelter's Syndrome

Physical Symptoms:

- Tall with Long arms and legs
- Wide hips
- Enlarged breasts (Gyecomastia)
- Sparse body hair
- Small testicles
- Less muscular
- Weaker bones

Klinefelter's Syndrome

Language Symptoms:

- Learn to talk late
- Trouble expressing thoughts and needs
- Problems reading
- Trouble processing what they hear

Other Symptoms:

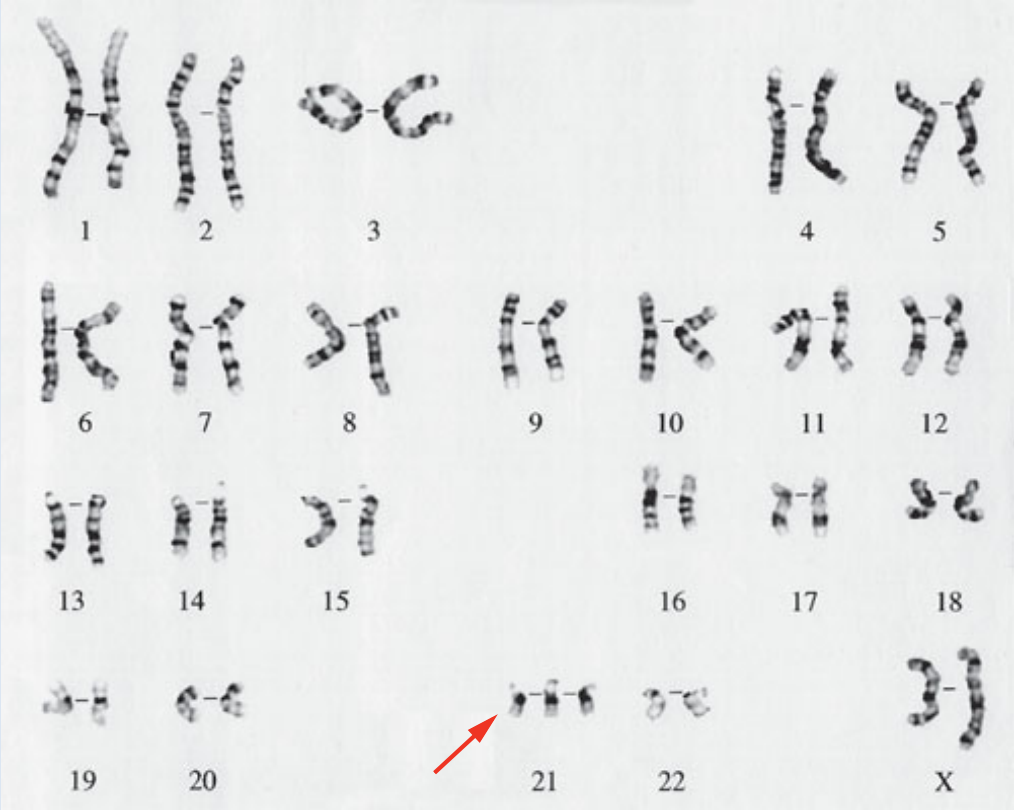
- Ambiguous sexual development (Intersexuality) and cannot father children
- Produce much less testosterone

3. Down syndrome

- 47,21+
- Trisomy 21: three copies of the genes on chromosome 21
- The parents of the affected individual are typically genetically normal

Down syndrome: cause

- **Nondisjunction**: failure of the 21st chromosome to separate during egg or sperm development.
- **Outcome**: sperm or egg cell is produced with an extra copy of chromosome 21; when combined with a normal cell from the other parent, the progeny has 47 chromosomes,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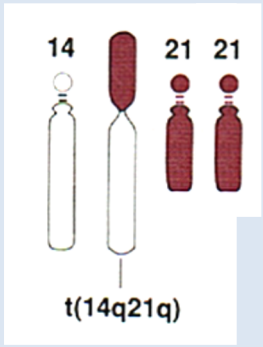
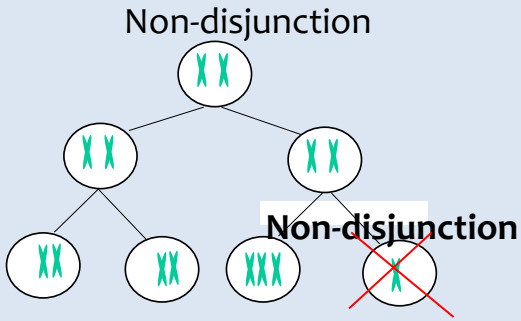
X

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)**

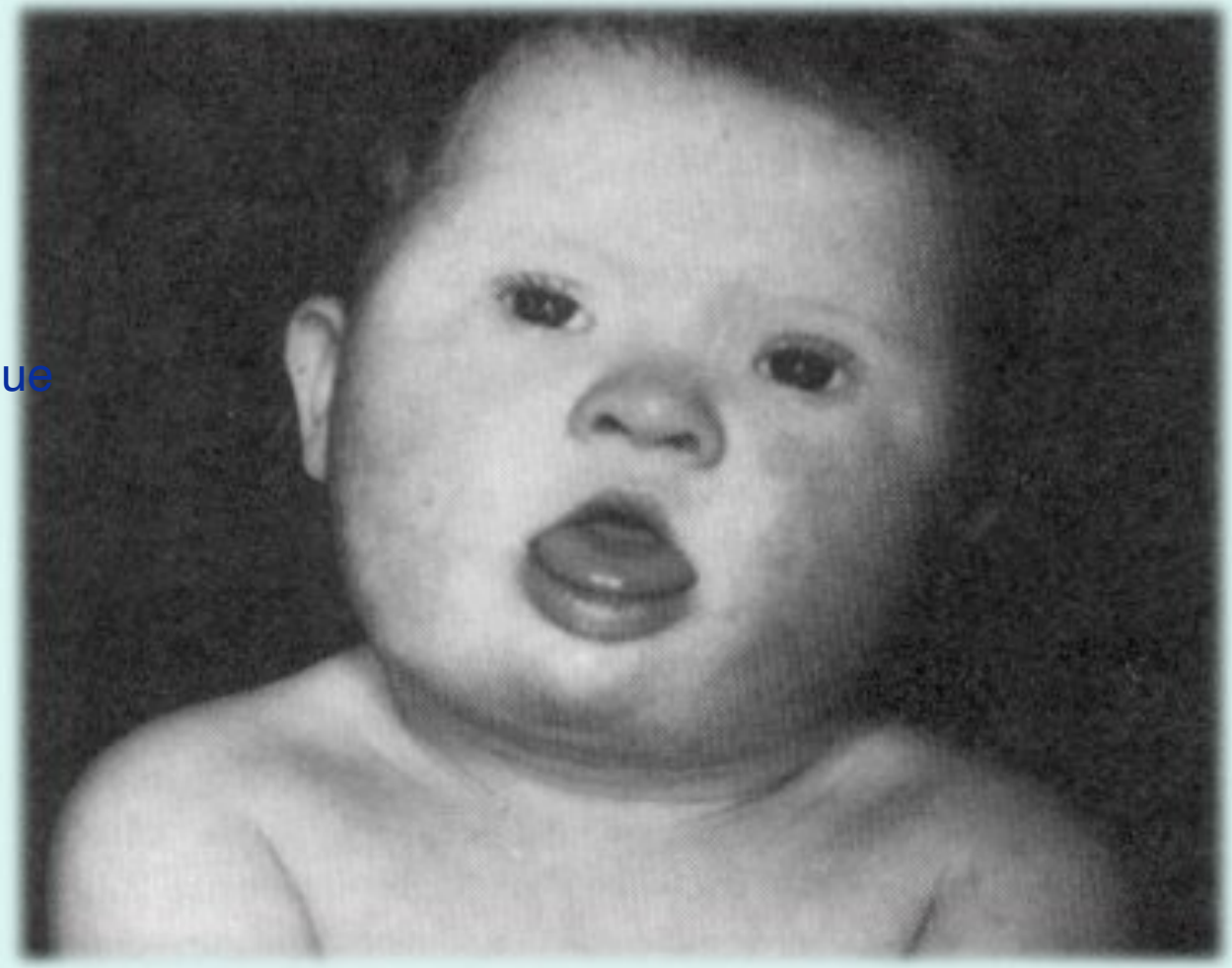


- 1% have **mosaicism** with normal and trisomy 21 cell lines (and usually have much milder features because of the presence of the normal cells); - occurs post zygotically

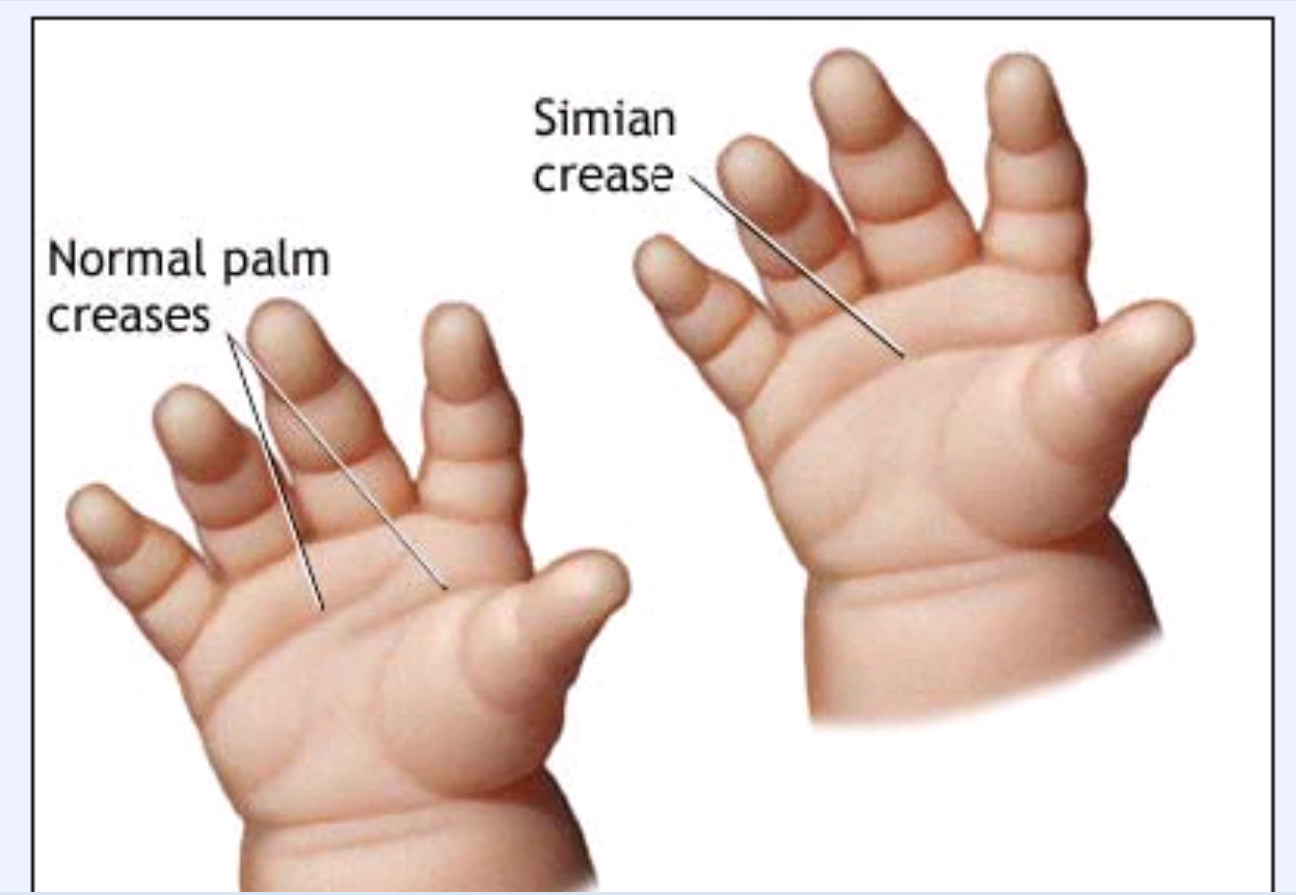
Down syndrome: symptoms

- short stature
- Mental impairment
- mild (IQ: 50–70) or moderate (IQ: 35–50) intellectual disability
- Stunted growth
- Epicanthic fold
- Slanted eyes
- Shortened hand
- Short neck
- Flat head
- Abnormal outer ear
- congenital heart disease
- a narrow pelvis
- rocker- bottom feet

Large Protruding tongue



Single transverse crease



Down syndrome

- Females may be fertile and may produce normal or trisomic progeny, but males do not reproduce.
- Mean life expectancy is about 17 years, and only 8 percent of persons with Down syndrome survive past age 40.

The incidence of Down syndrome is related to maternal age; older mothers have more risk of having a child with Down syndrome

chromosome analysis of fetal cells is done in high risk females

a. Amniotic fluid (amniocentesis) or
b. Chorion of placenta(chorionic villus sampling CVS OR
c. Maternal circulation Non invasive prenatal genetic diagnosis NIPGD)

About 88% of cases of trisomy 21 result from nonseparation of the chromosomes in the mother, 8% from nonseparation in the father

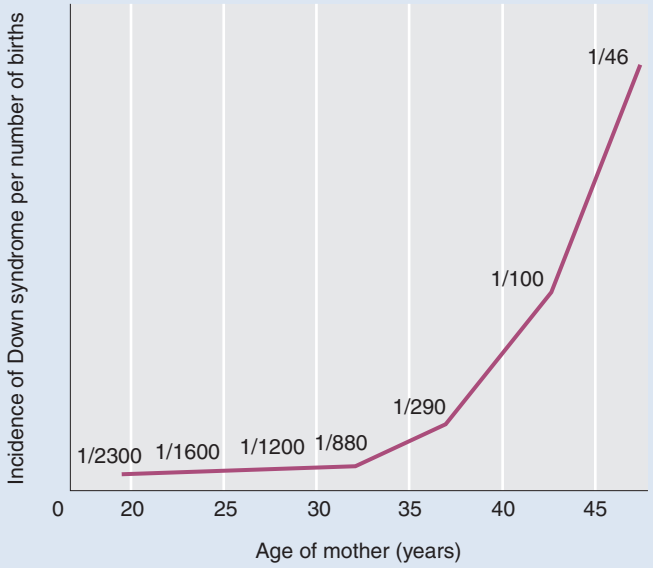


Figure 15-18 Maternal age and the production of offspring with Down syndrome. [From L. S. Penrose and G. F. Smith, *Down's*

Molecular mechanisms: female meiosis appears to be more error prone?

male

- Human Male gametes quickly go through all stages of meiosis I and II.

female

- In Female, oocytes are arrested at diplotene (prophase I) before birth.
- Meiosis resumes at each ovulatory cycle, hence, the chromosomes in the tetrad remain associated for several decades.

Factors contributing to non-disjunction

male

- In males, the cohesin protein complex is stable and **keeps sister chromatids together** and provides binding sites for proper spindle attachment.

female

- Prolonged arrest of oocytes in females, lead to **weakening and loss of cohesin ties** causing incorrect microtubule-kinetochore attachment and chromosome segregation errors during meiotic divisions.

Factors contributing to non-disjunction

male

- In males, almost all chromosome pairs are joined by at least one crossover preventing non-disjunction

female

- More than 10% of human oocytes in females show atleast one bivalent without any crossover event.
- This failure of recombination or inappropriately located crossovers contributes to non-disjunction

Down syndrome critical region DSCR

a region on chromosome 21 has been identified that is sensitive to trisomy and results in its typical phenotypes.

- A mouse model was created in 2004 that is trisomic for the DSCR

DSCR1 encodes a protein that suppresses VEGF (vascular endothelial growth factor).

Suppression of VEGF blocks angiogenesis

overexpression of this gene inhibits tumors from forming proper vascularization, limiting their growth

individuals show decreased risk of developing cancers e.g.lung cancer and melanoma.