Medical Genetics

Klinefelter, Turner & Down Syndrome

Reproductive Block, 2020

Lecture Objectives:

By the end of this lecture, the students should be able to:

- Describe cell cycle and stages of Mitosis and Meiosis
- Define nondisjunction and describe its consequences for meiosis and mitosis.
- Classify chromosomal abnormalities
- Understand the common numerical chromosomal disorders: monosomy and trisomy
- Understand the common numerical autosomal & sex chromosome disorders: Down, Turner & Klinefelter syndromes

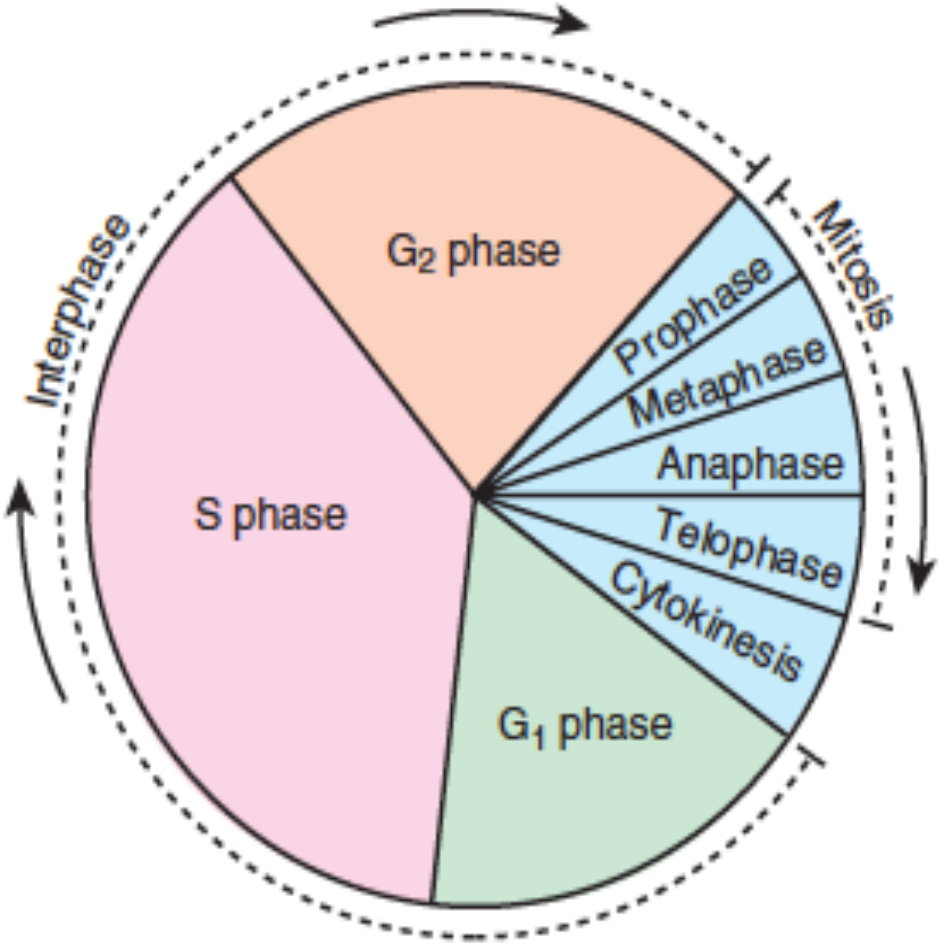
The cell cycle

Cellular components are replicated = **Interphase**

Cell distributes its contents into two daughter cells = **Mitosis**

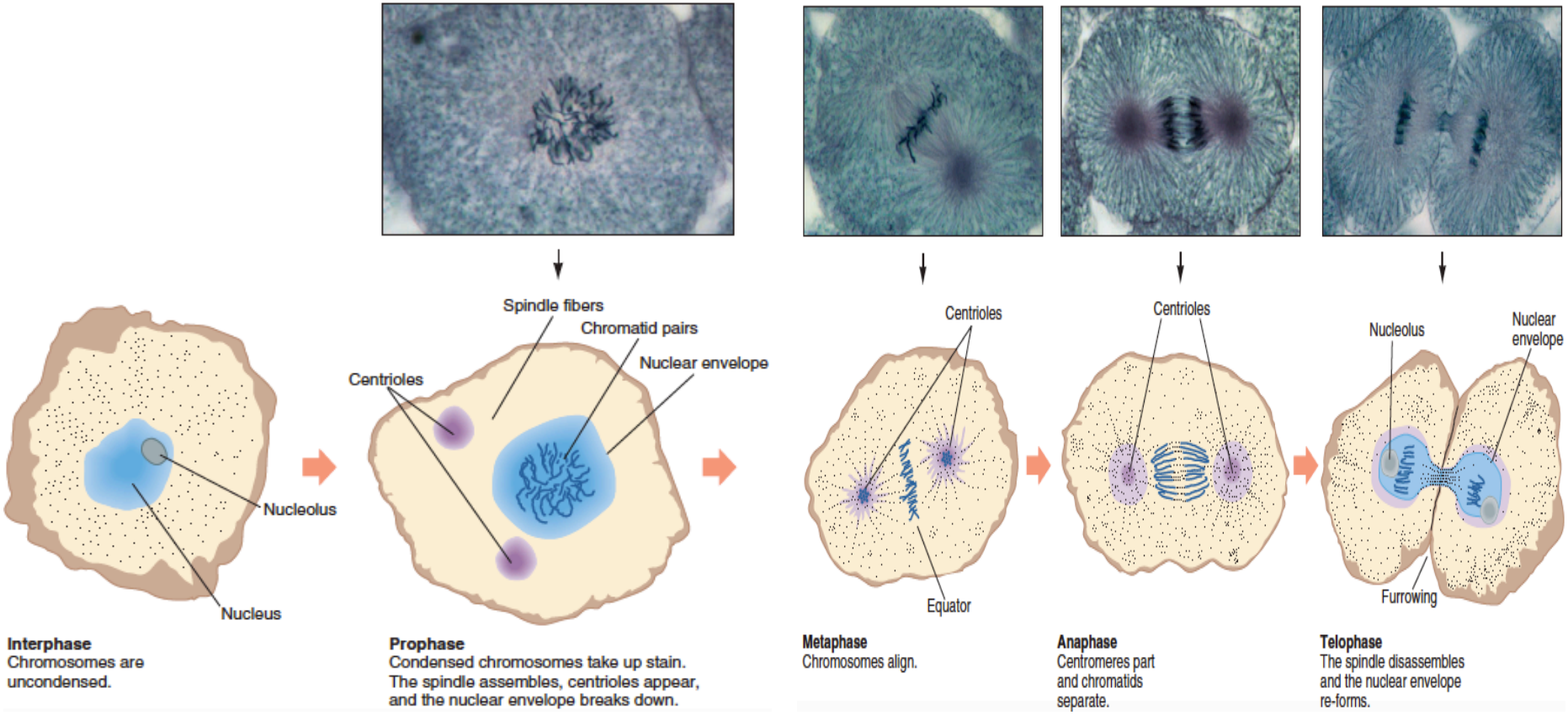
G1 and G 2 = cell duplicates specific molecules and structures

S phase = cell replicates DNA



Stages of Mitosis & Meiosis

Mitosis in a human cell



Interphase
Chromosomes are uncondensed.

Prophase
Condensed chromosomes take up stain. The spindle assembles, centrioles appear, and the nuclear envelope breaks down.

Metaphase
Chromosomes align.

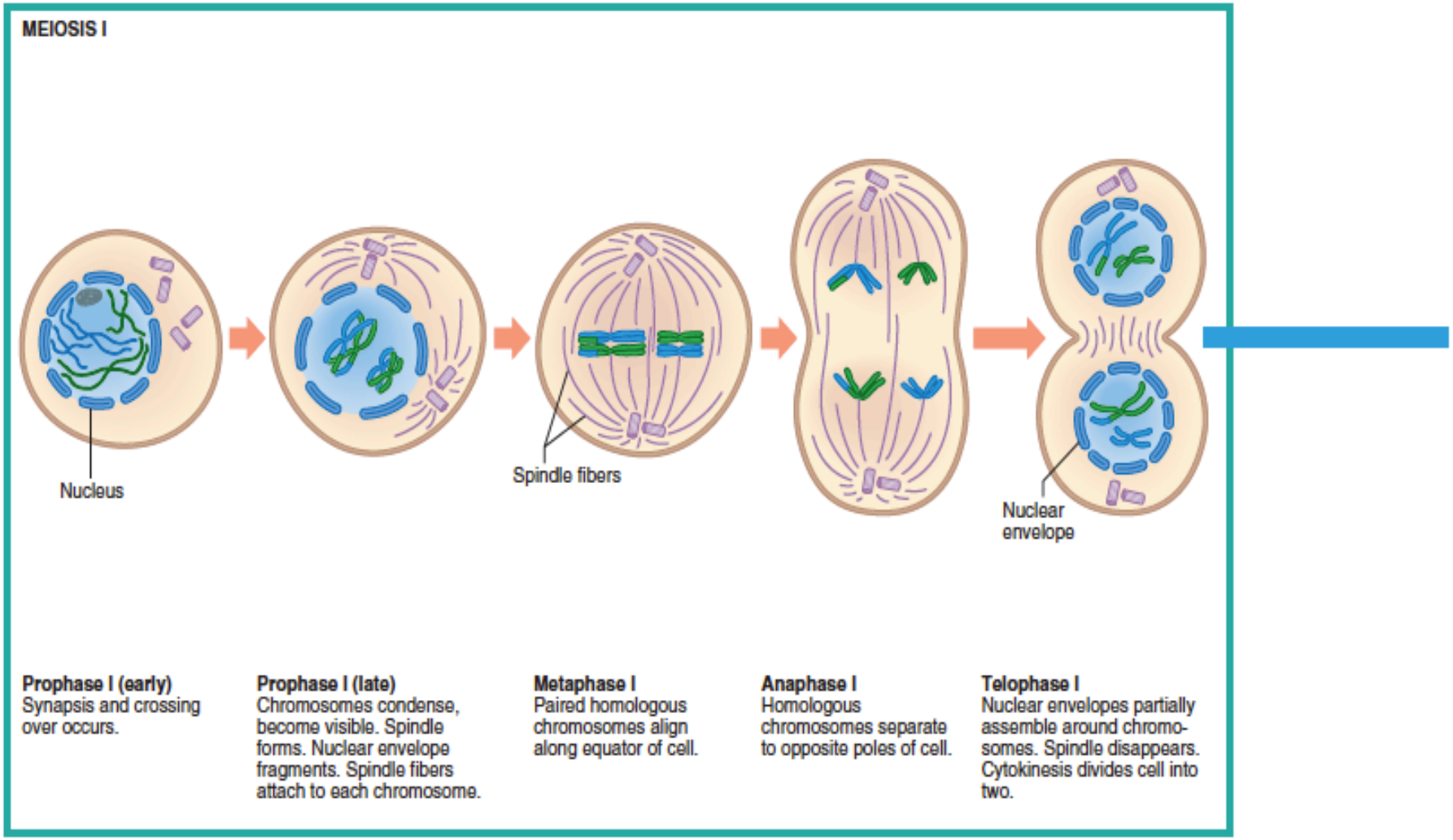
Anaphase
Centromeres part and chromatids separate.

Telophase
The spindle disassembles and the nuclear envelope re-forms.

Stages of Mitosis & Meiosis

Stages of Meiosis

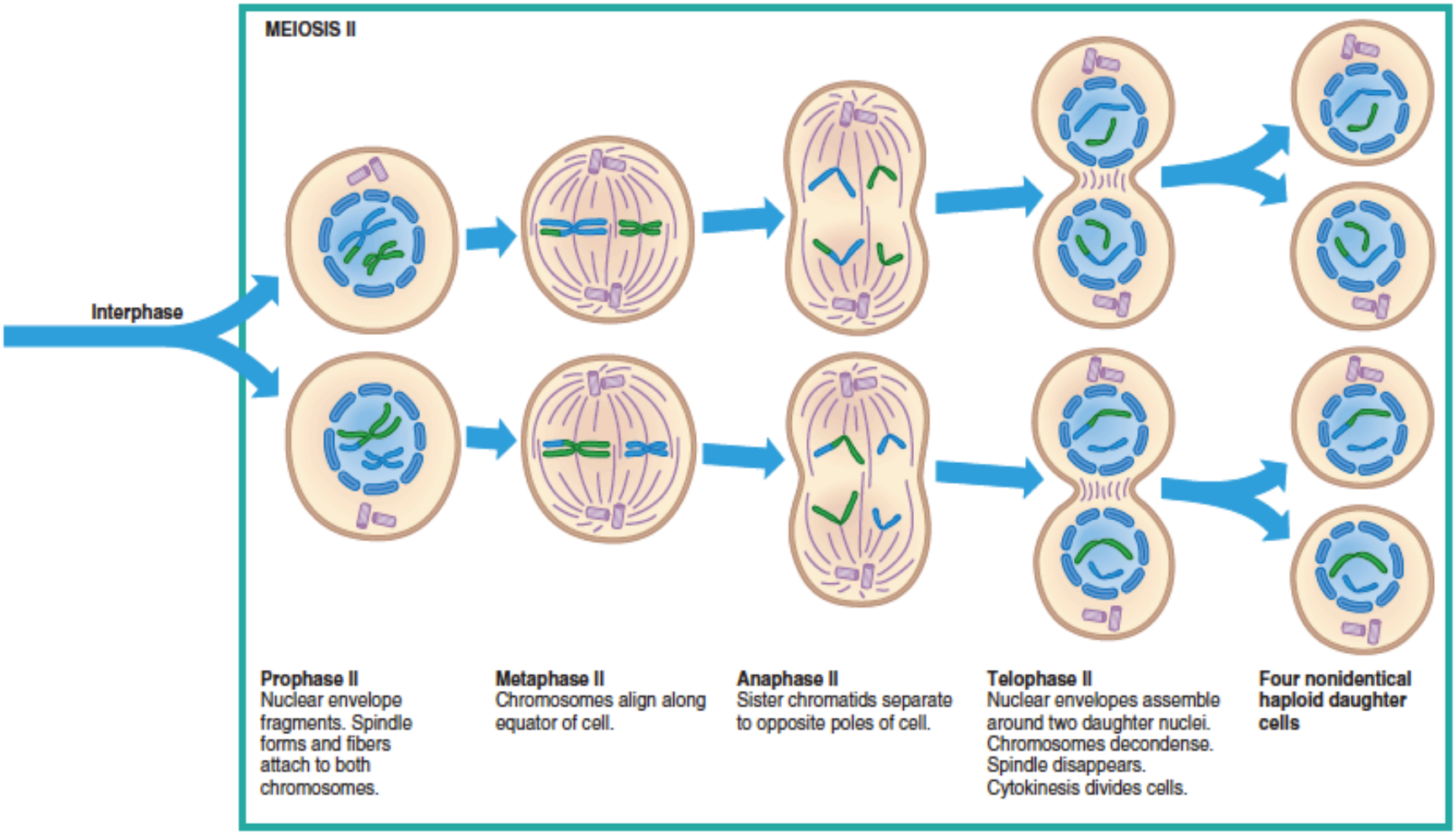
Meiosis I



Stages of Mitosis & Meiosis

Stages of Meiosis

Meiosis II



Comparison of Mitosis and Meiosis

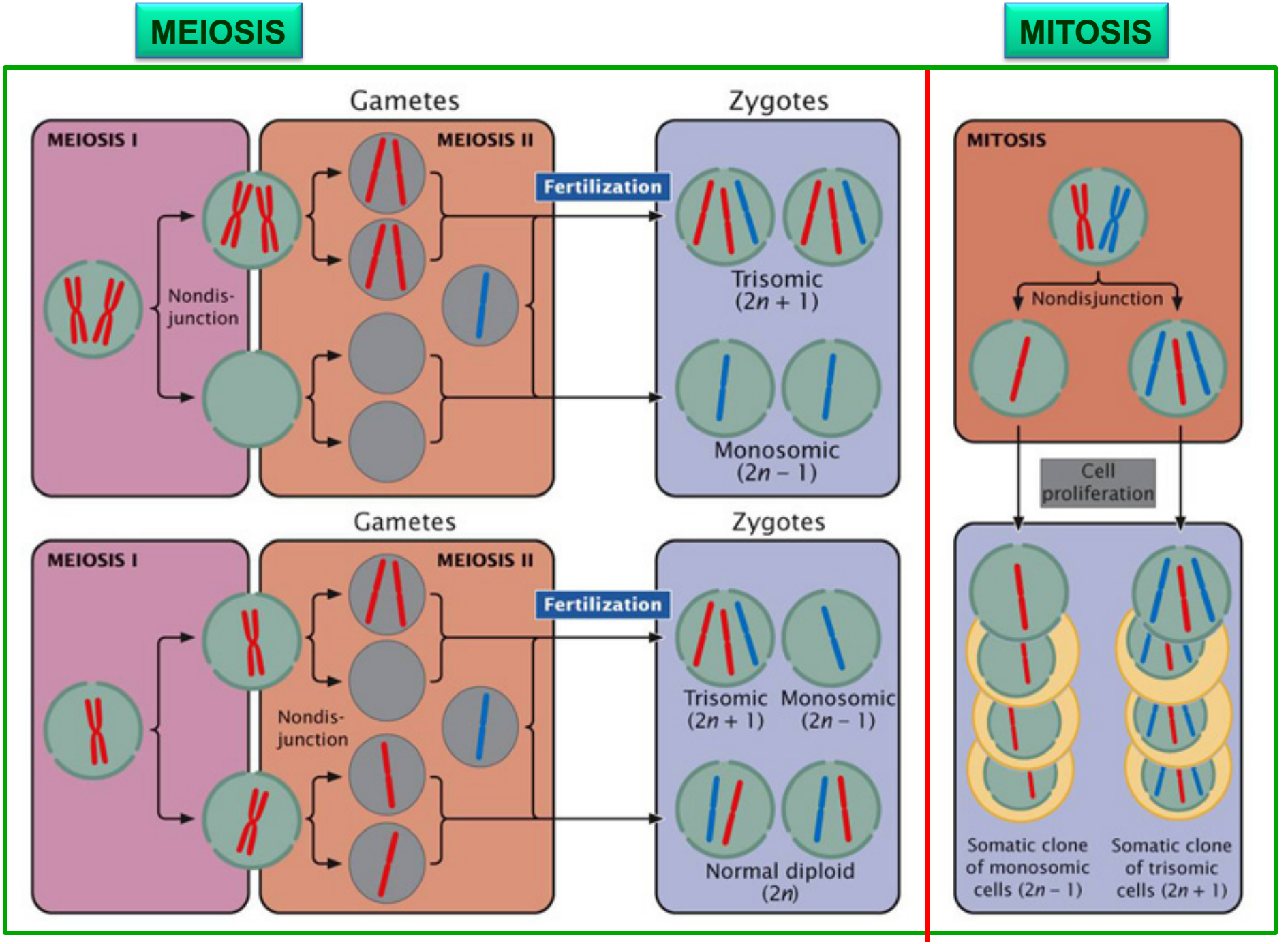
Mitosis	Meiosis
One division	Two divisions
Two daughter cells per cycle	Four daughter cells per cycle
Daughter cells genetically identical	Daughter cells genetically different
Chromosome number of daughter cells same as that of parent cell (2*n*)	Chromosome number of daughter cells half that of parent cell (1*n*)
Occurs in somatic cells	Occurs in germline cells
Occurs throughout life cycle	In humans, completes after sexual maturity
Used for growth, repair, and asexual reproduction	Used for sexual reproduction, producing new gene combinations

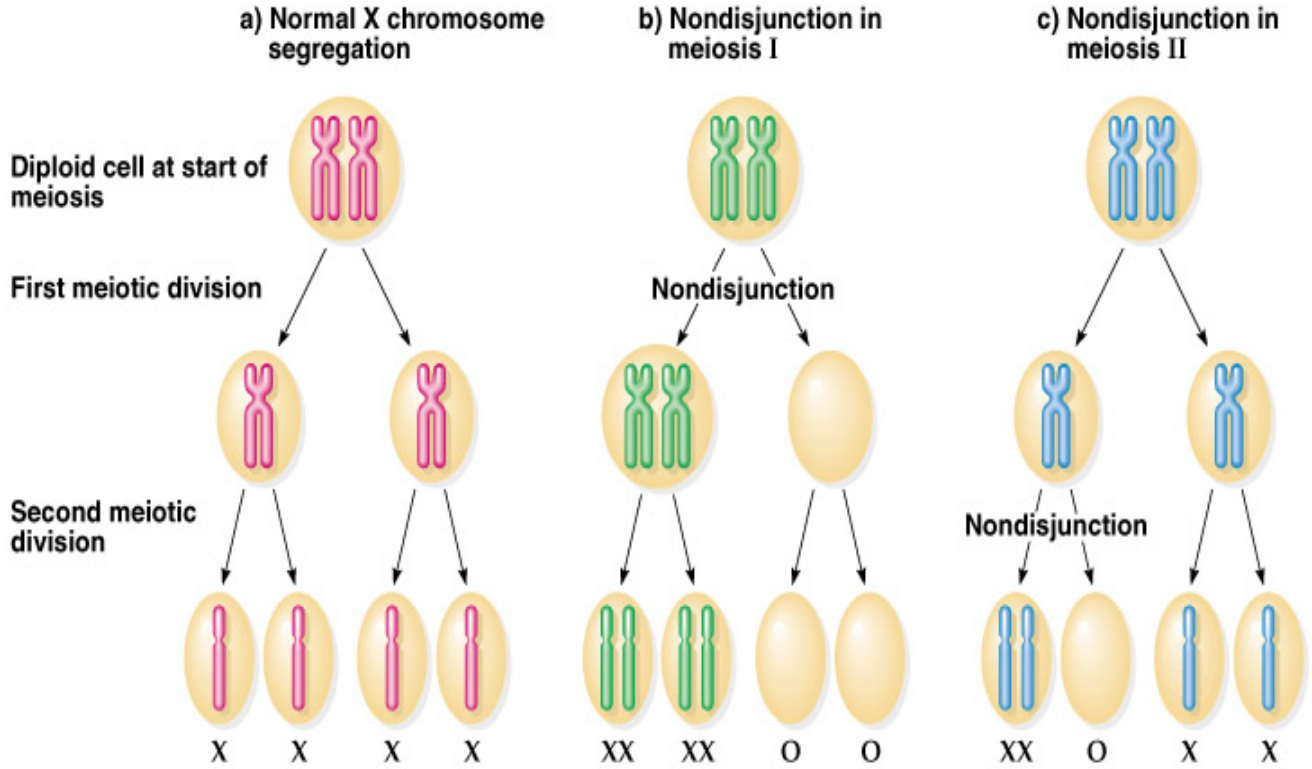
Summary of the chromosome and chromatid number during Mitosis, MeiosisI & II in humans:

Phase (Mitosis)	# Chromosomes	# Chromatids
Prophase	46	92
Metaphase	46	92
Anaphase	92	92
Telophase	92	92
End of Mitosis (separated cells)	46	46
Phase (Meiosis I)	# Chromosomes	# Chromatids
Prophase I	46	92
Metaphase I	46	92
Anaphase I	46	92
Telophase I	46	92
End of Meiosis I (separated cells)	23	46
Phase (Meiosis II)	# Chromosomes	# Chromatids
Prophase II	23	46
Metaphase II	23	46
Anaphase II	46	46
Telophase II	46	46
End of Meiosis II (separated cells)	23	23

Nondisjunction in Meiosis

- Nondisjunction "not coming apart" is the failure of a chromosome pair to separate properly during meiosis 1, or of two chromatids of a chromosome to separate properly during meiosis 2 or mitosis.
- Can affect each pair of chromosomes
- Is not a rare event
- As a result, one daughter cell has two chromosomes or two chromatids, and the other has none.
- The result of this error is a cell with an imbalance of chromosomes (Aneuploidy)


MEIOSIS
MITOSIS
Gametes
Zygotes
MEIOSIS I
MEIOSIS II
Nondis-
junction
Fertilization
Trisomic
(2n + 1)
Monosomic
(2n – 1)
MITOSIS
Nondisjunction
Cell
proliferation
Gametes
Zygotes
MEIOSIS I
MEIOSIS II
Nondis-
junction
Fertilization
Trisomic
(2n + 1)
Monosomic
(2n – 1)
Normal diploid
(2n)
Somatic clone
of monosomic
cells (2n – 1)
Somatic clone
of trisomic
cells (2n + 1)



4 haploid gametes

2 gametes with diploid number of X chromosome, and 2 gametes lacking X chromosome

2 gametes with haploid number of X chromosome, 1 gamete with diploid number of X chromosome, and 1 gamete lacking X chromosome

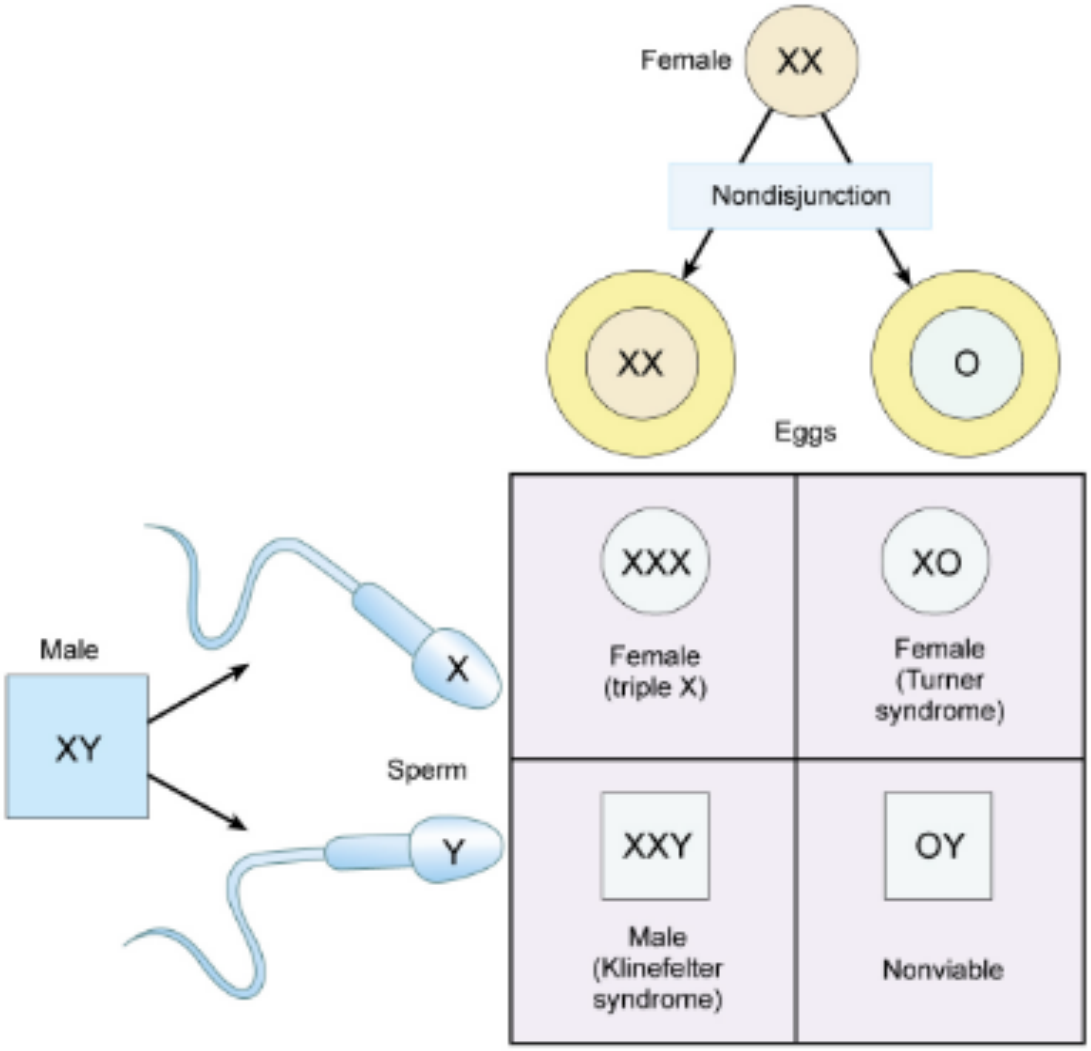
Aneuploidy

Autosomal:

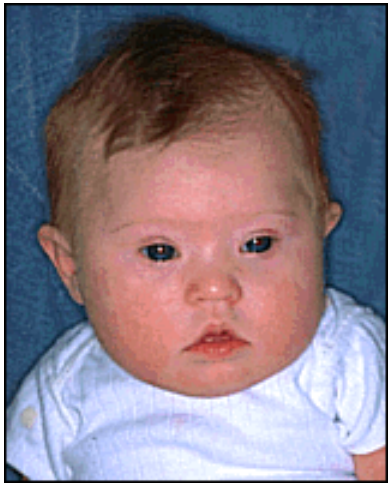
- Trisomy 21 (Down syndrome)

Sex chromosome

- 47XXY (Klinefelter syndrome)
- 45X (Turner syndrome)

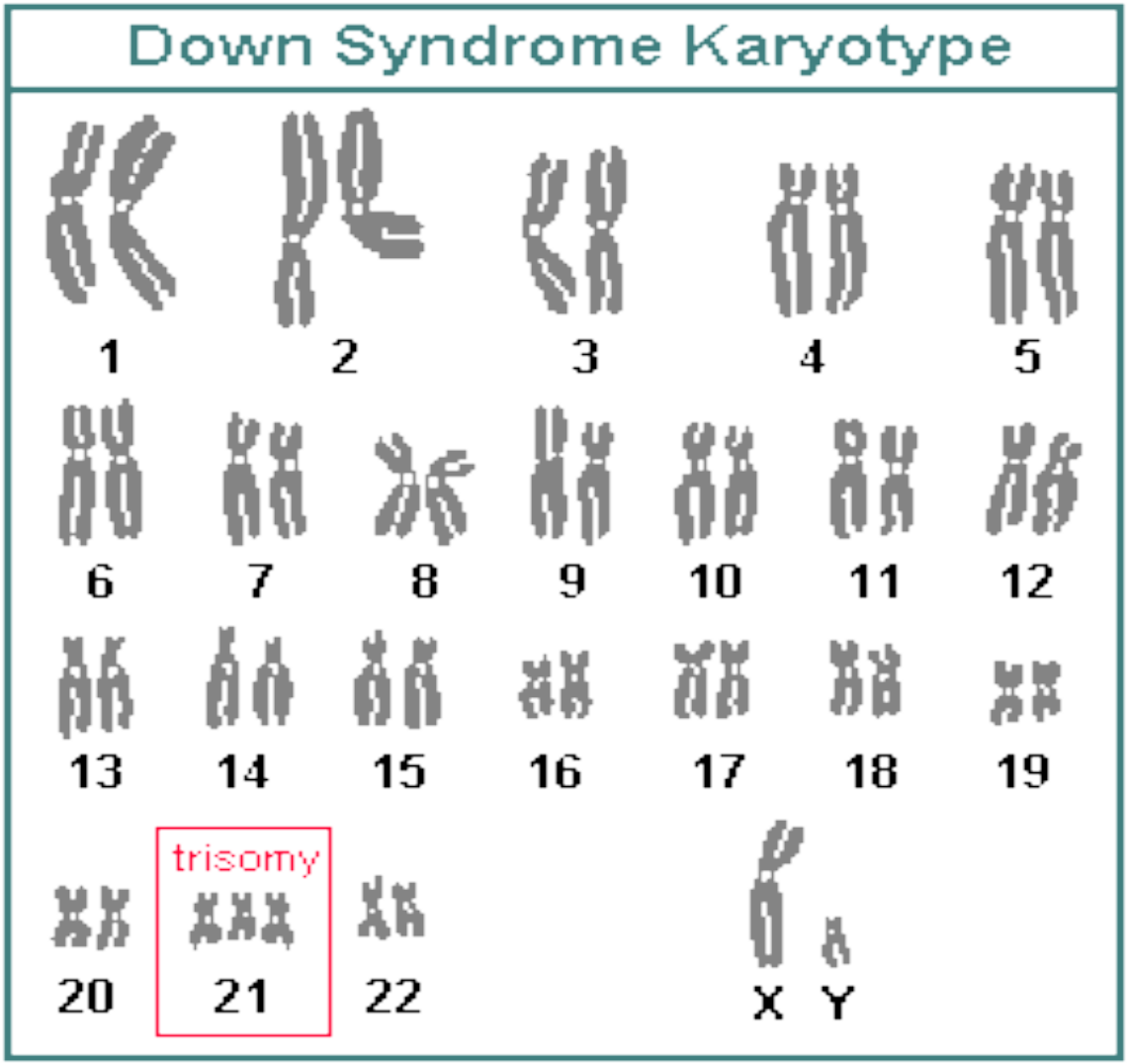


Down Syndrome

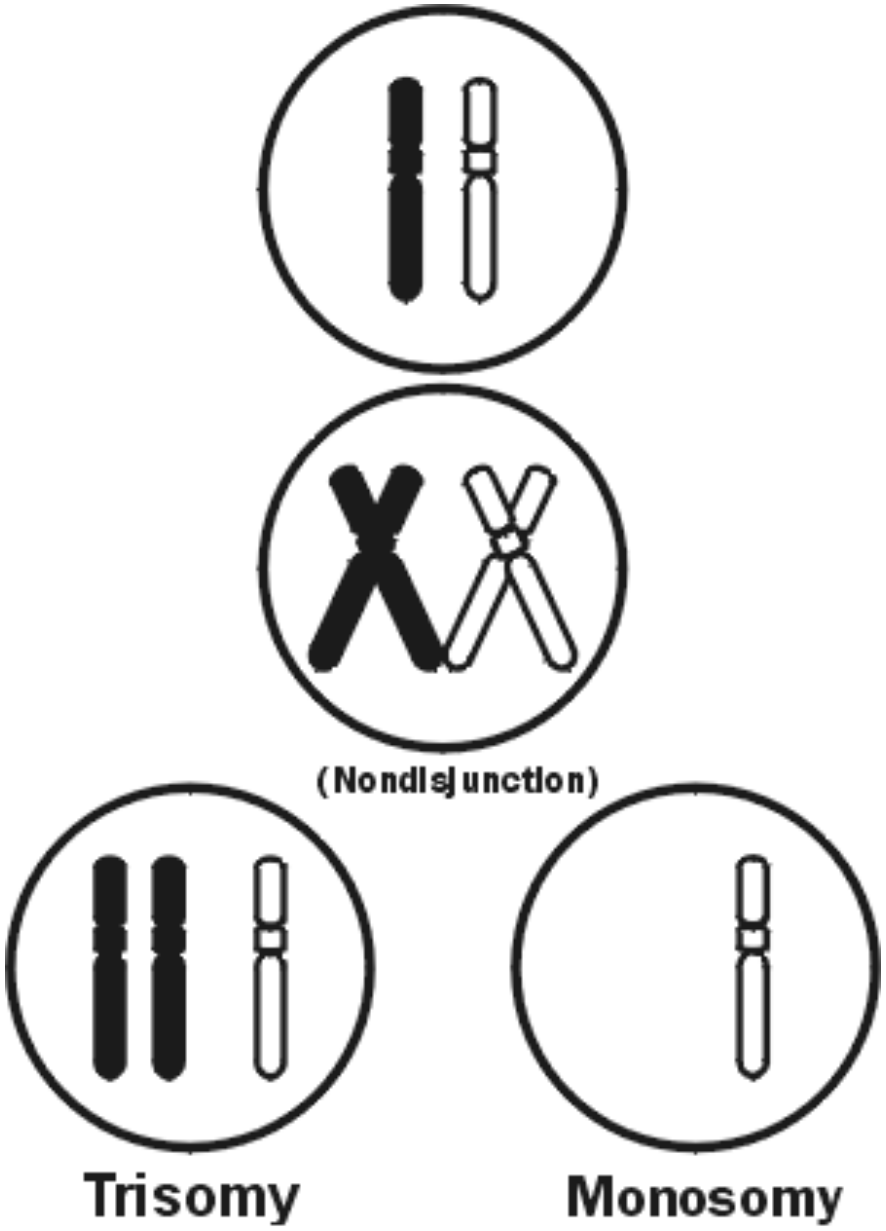


Down Syndrome

- Three copies of chromosome 21



3 copies
=
trisomy



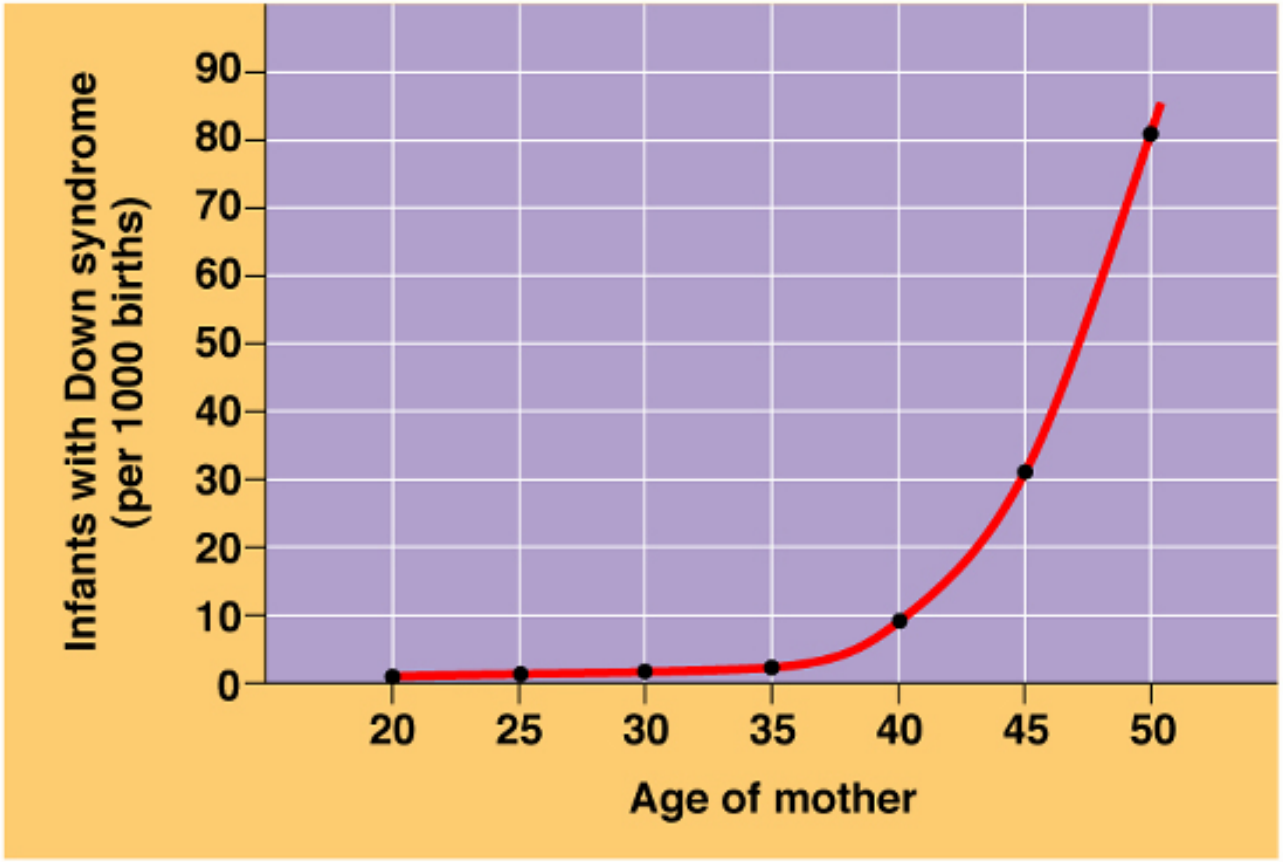
1 copy =
monosomy

Down syndrome, trisomy 21

Karyotype: 47,XY,+21

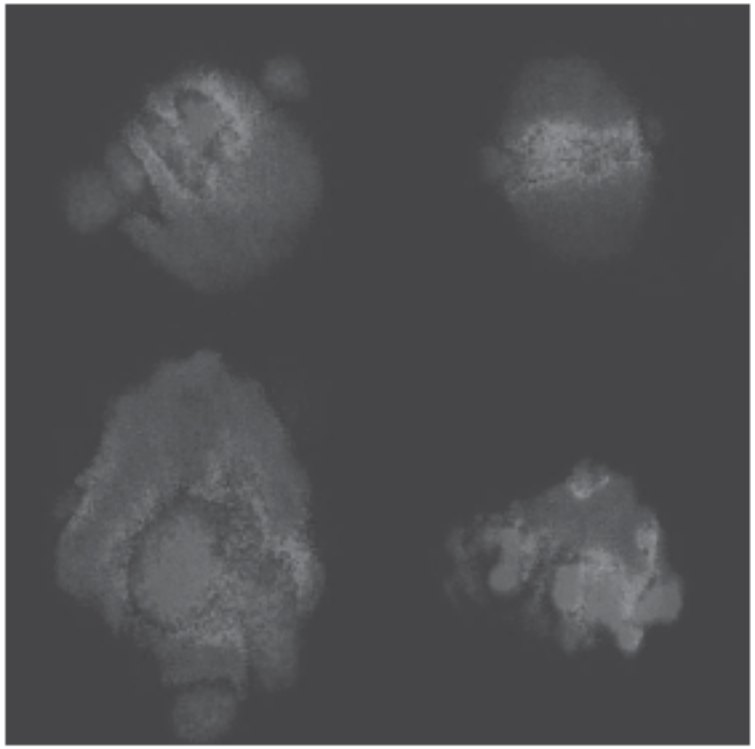
- **Most cases arise from nondisjunction restricted to meiotic errors in the egg**
- **Mothers are the source of the extra chromosome in the majority of cases.**
- **advanced maternal age was significantly associated with both meiosis I (MI) and meiosis II (MII)**
- nondisjunction occurred in MII, mothers were 15.1 times more likely to be ≥40 years compared to 8.5 times of nondisjunction in MI
- **A small proportion of cases are mosaic and these probably arise from a nondisjunction event in an early zygotic division = mitotic**

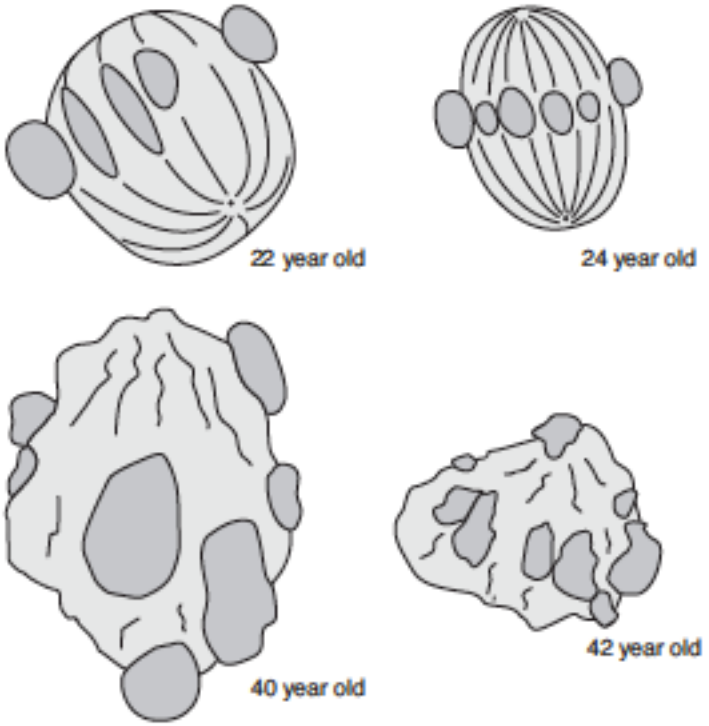
Down Syndrome



The incidence of trisomy 21 rises sharply with increasing maternal age

Meiosis II oöcytes from younger and older women





Features of Down Syndrome

- Low muscle tone = loose and floppy side
- Head and facial malformations: (Small round face, protruding tongue = Sticks to the mouth floor)
- Abnormalities of the extremities: (Short and broad hands, Stubby fingers), single deep crease across the center of the palm
- Developmental delays (mental retardation)
- Heart malformations
- Impotency in males = Inability to sustain an erection sufficient for sexual intercourse or the inability to ejaculate
- Life expectancy increased from 25 in 1983 to 60 today

Sex chromosome imbalance is much less deleterious

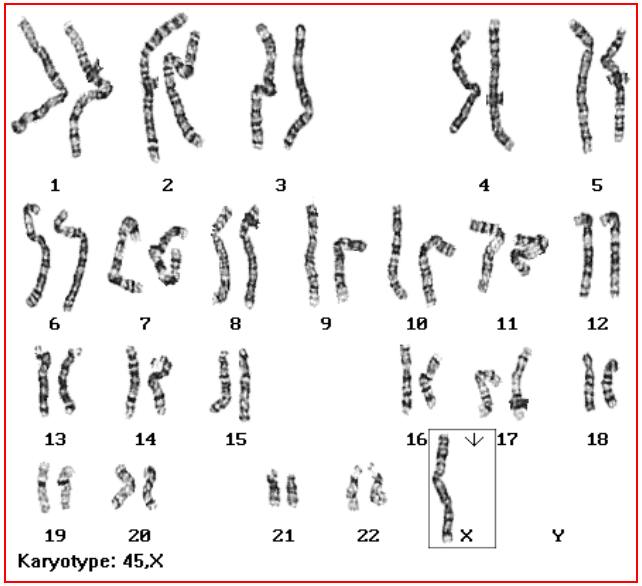
1.Klinefelter Syndrome (47,XXY)

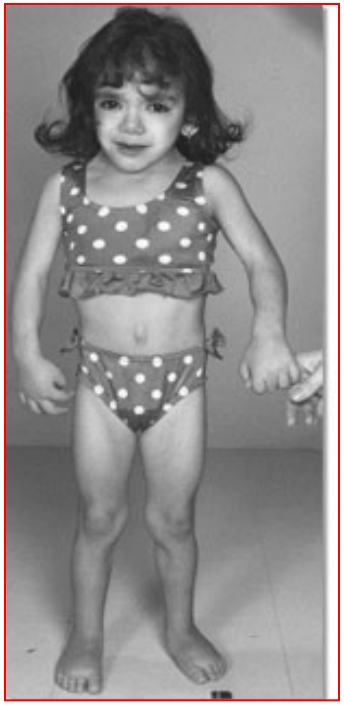
2.47,XYY Syndrome (May be without any symptoms. Males are tall but normally proportioned. 10 - 15 points reduction in IQ compared to sibs)

3.Trisomy X (47,XXX) females: (It seems to do little harm, individuals are fertile and do not transmit the extra chromosome. They do have a reduction in IQ comparable to that of Klinfelter males)

4.Turner Syndrome (45,X and variants)

Turner syndrome (Monosomy X: 45, XO) and variants





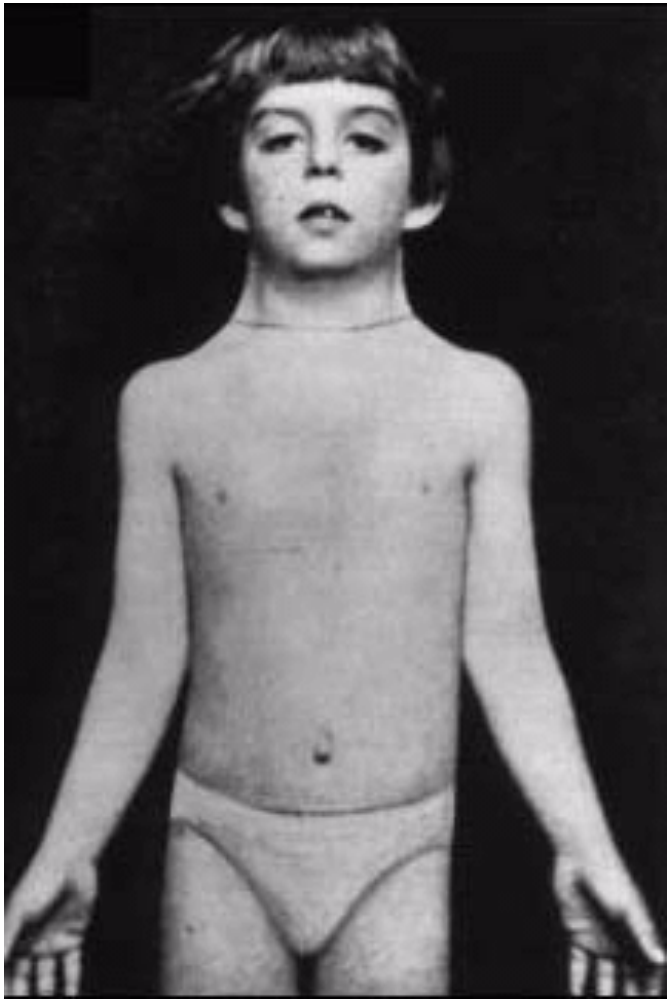
Turner Syndrome

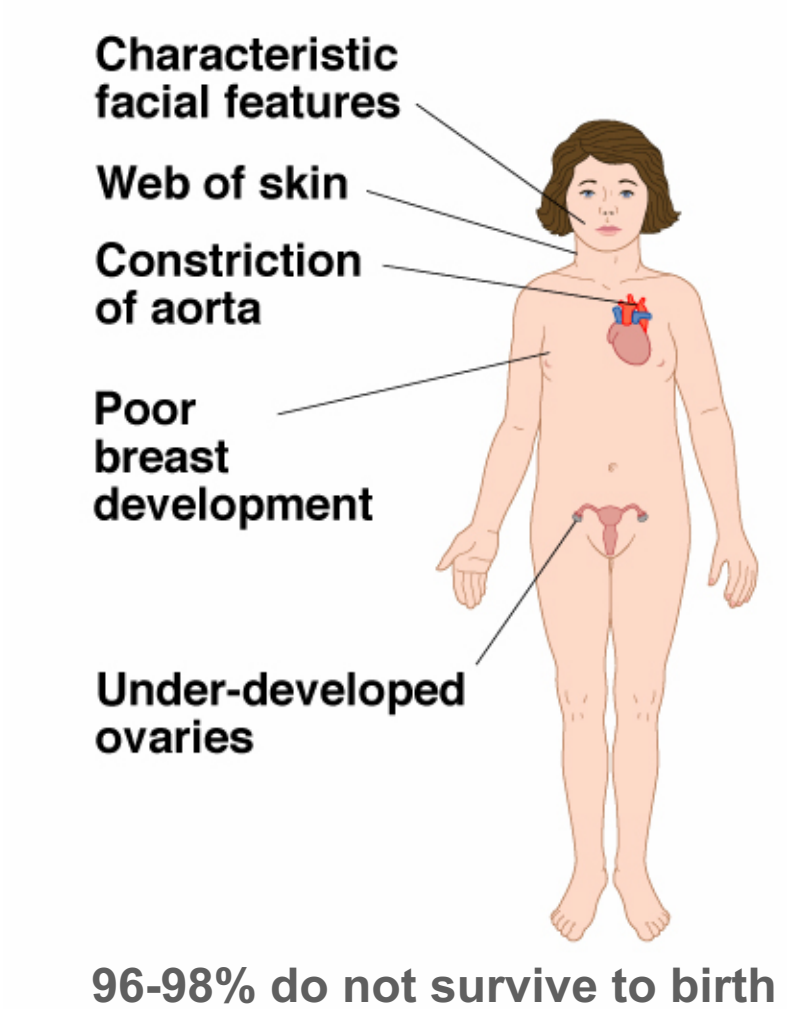
- Monosomy of sex chromosome: (Monosomy X: 45, XO) i.e. only one X chromosome is present.
- Occurrence – 1 in 2500 live female births
- The only viable monosomy in humans
- Individuals are genetically female, not mature sexually and sterile

Features of Turner Syndrome

- Short stature, Broad chest, Low hairline
- Neck abnormalities (webbed neck)
- Skeletal disorders (e.g. scoliosis, dislocated hips/elbows)
- Lack of ovarian development (Streak ovaries)
- Increased risk of osteoporosis, cardiovascular anomalies
  e.g. constriction of aorta and hypertension
- No developmental delays, Normal intelligence
- Normal life span

XO – Turner Syndrome

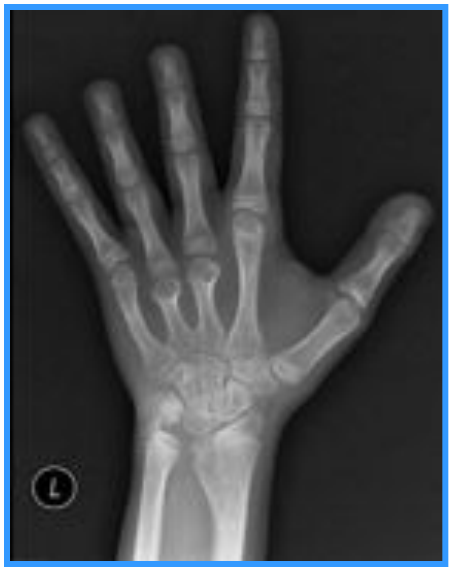




96-98% do not survive to birth

Features of Turner Syndrome,

Continued…



Cardiovascular

Bicuspid aortic valve

Coarctation of aorta

Thoracic aortic aneurysm (aortic root dilatation)

Skeletal

Short stature

Short 4th metacarpal/metatarsal bone (± short 3rd and 5th)

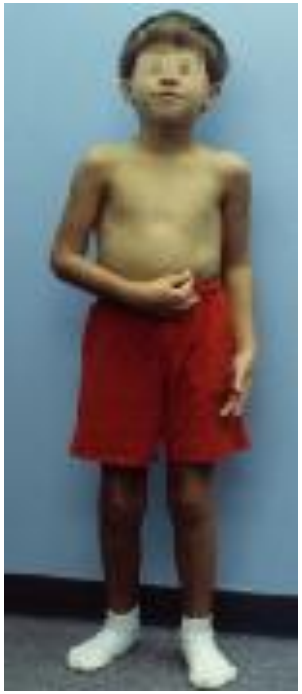
Osteoporosis (due to lack of estrogen)

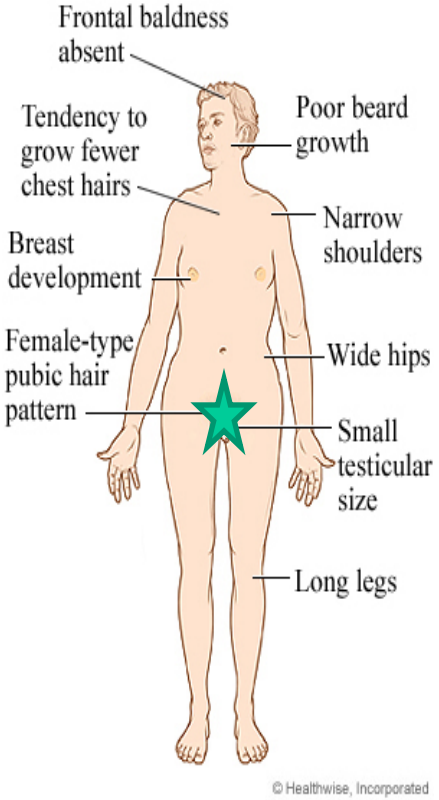
Scoliosis

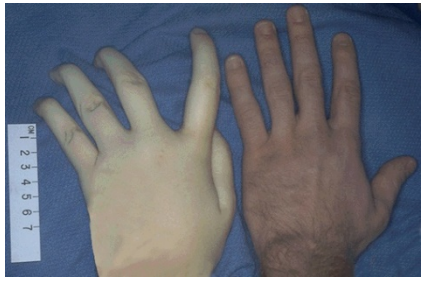
Reproductive

Women with Turner syndrome are almost universally infertile

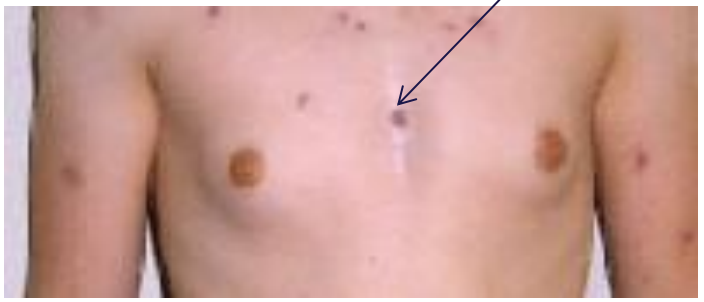
Klinefelter Syndrome







Brown spots (nevi)

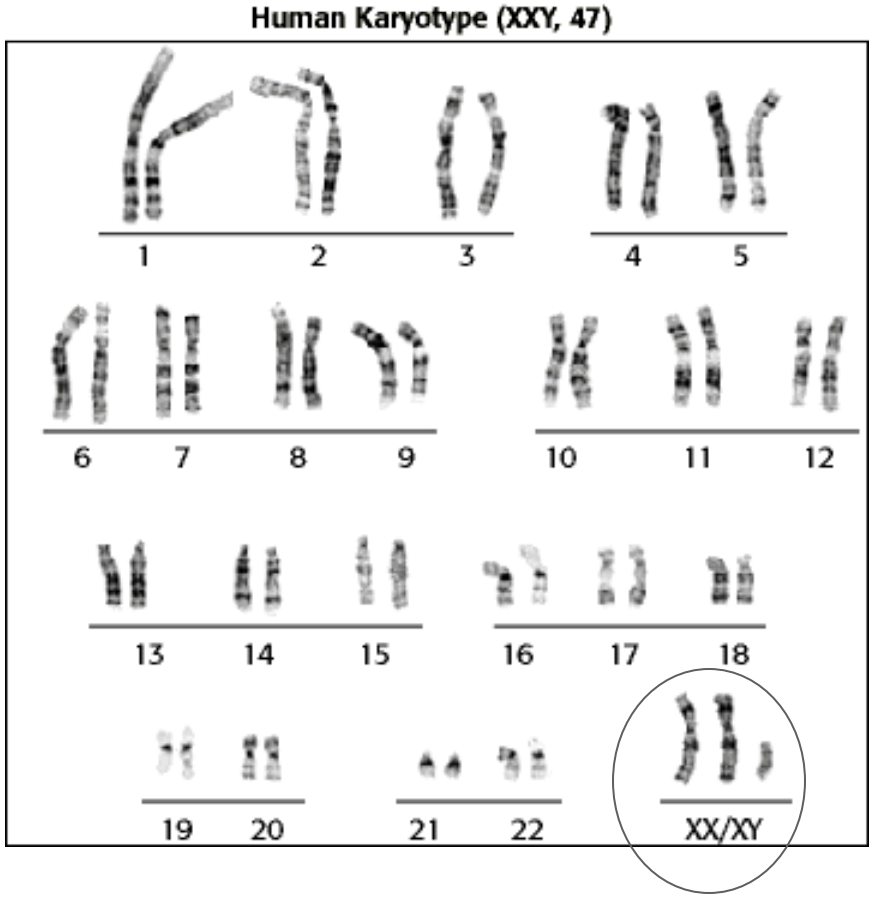


Klinefelter Syndrome

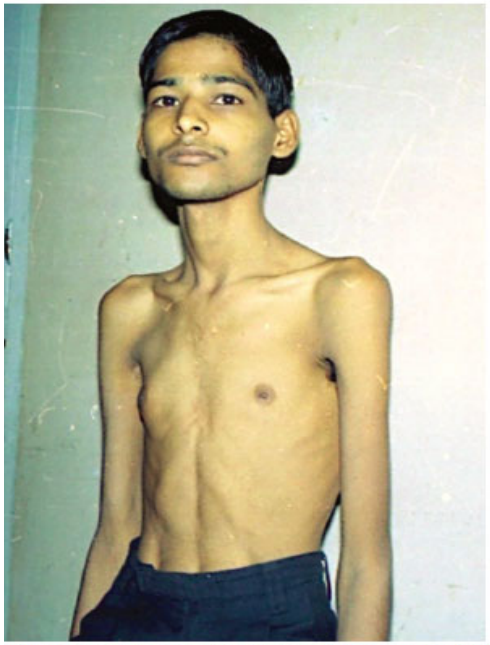
1 in 1,100 births

47 chromosomes

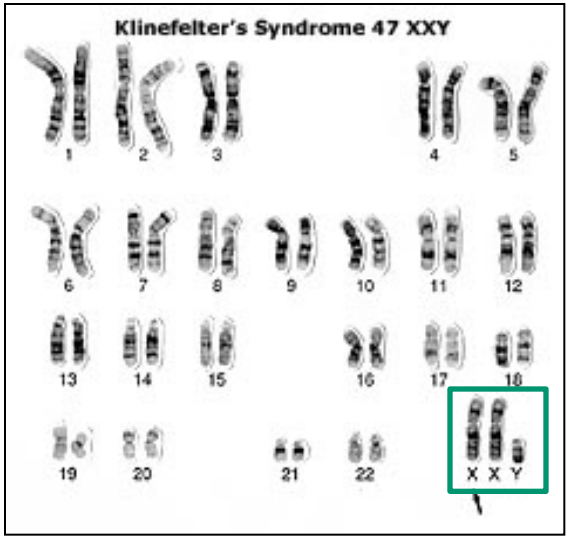
47, XXY



Klinefelter Syndrome: 47,XXY males



: Photograph showing development of gynecomastia in a
old male after 2 months of isoniazid containing Categor
ATT



Features of Klinefelter Syndrome

- Tall
- Sexually underdeveloped & infertile* (no spermatogenesis)
- Sparse facial and body hair
- Delays in speech and motor skills
- Deficits in attention, auditory processing and social skills.
- Low mental ability (slight reduction in IQ, but usually normal intelligence)

* In some cases testicular function is preserved

Features of Klinefelter Syndrome, *continued…*

- Longer fingers and arms
- Delicate skin
- Gynaecomastia and other feminine body characteristic
- Increased risk of autoimmune disorders, breast cancer, osteoporosis, leg ulcers, depression, and dental problems
- Normal life span
- Very rarely more extreme forms of Klinefelter syndrome occur where the patient has 48, XXXY or even 49, XXXXY karyotype. These individuals are generally severely retarded.
- Treatment includes testosterone therapy and assisted learning

When to do a chromosomal test

- **Prenatal**:

- Maternal age>37yrs;

- Ultrasound scan (USS) changes

- Triple test:

- measuring the alpha fetoprotein (AFP) = detect the vast majority of neural tube defects and and a small portion of trisomy 21–affected pregnancies

- human chorionic gonadotropin (hCG), and estriol: if positive it indicates an increased risk of trisomy 21 and 18

- **Postnatal:**

Learning & developmental disability; growth retardation

- **Infertility:**

Recurrent miscarriage, primary infertility

Rapid Aneuploidy Screening by Fluorescence in situ hybridization (FISH)

- Available on amniocentesis sample
- Uncultured amniocytes
- FISH probes for X,Y, 21
- Result in 24-48 hours
- Proceed onto full karyotype (11-14 days)

New techniques

- Quantitative Fluorescence PCR (qf PCR): is able to measure number of copies of a chromosome – used for trisomy screening

- Cell-free fetal DNA from maternal plasma – at 6-8 weeks of gestation. It is a non-invasive prenatal diagnostic tool for chromosomal aneuploidy. It can be used to determine the fetus sex–: look for presence of Y chromosome material

Take home message

- Normal human karyotype is 46,XY or 46,XX
- Chromosome abnormalities can be numerical or structural
- Numerical abnormalities include aneuploidy and polyploidy
- In monosomy or trisomy, a single extra chromosome is absent or present, usually as a result of nondisjunction in the 1st or 2nd meiotic division
- Structural abnormalities include translocations, inversions, deletions, isochromosome & rings

THANK YOU!