Medical Genetics

Klinefelter, Turner & Down Syndrome

Reem Sallam, *MD, PhD*

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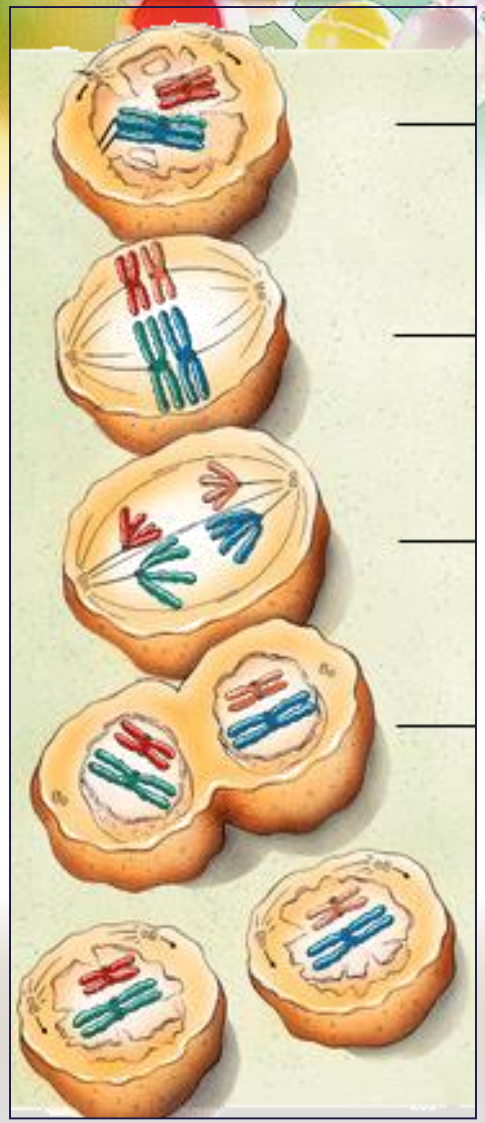
Lecture Objectives:

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

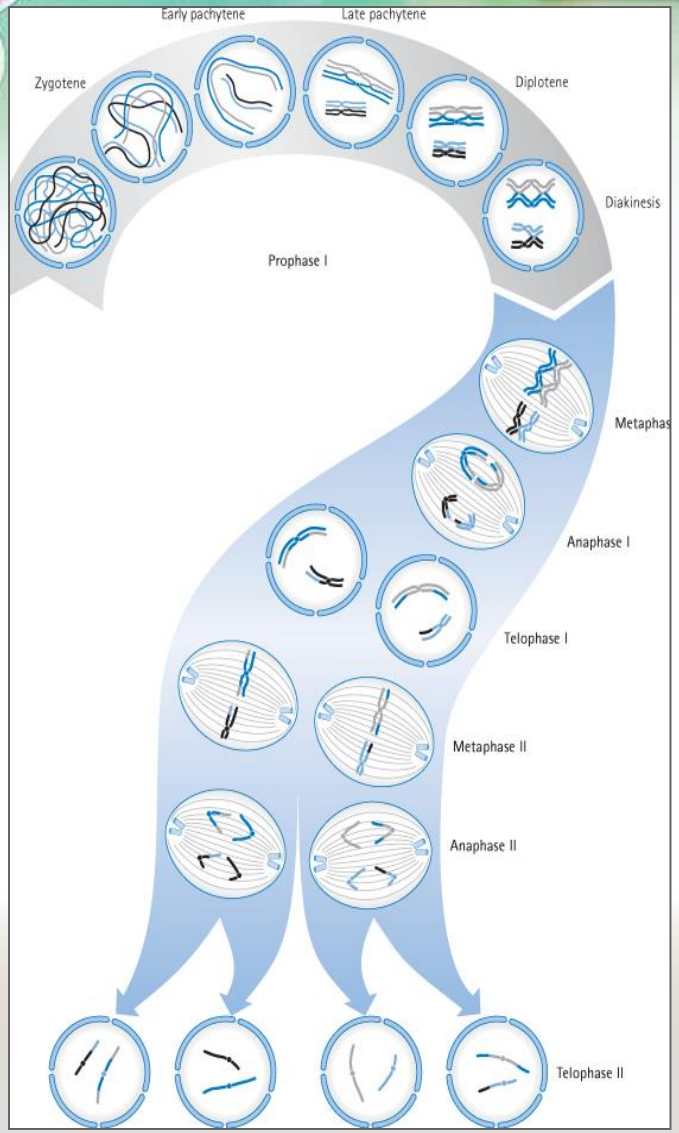
- Define nondisjunction and describe its consequences for meiosis and mitosis.
- Classify chromosomal abnormalities
- Understand the common numerical chromosomal disorders: monosomy and trisomy
- Understand the common numerical sex chromosome disorders: Down , Turner & Klinefelter syndromes

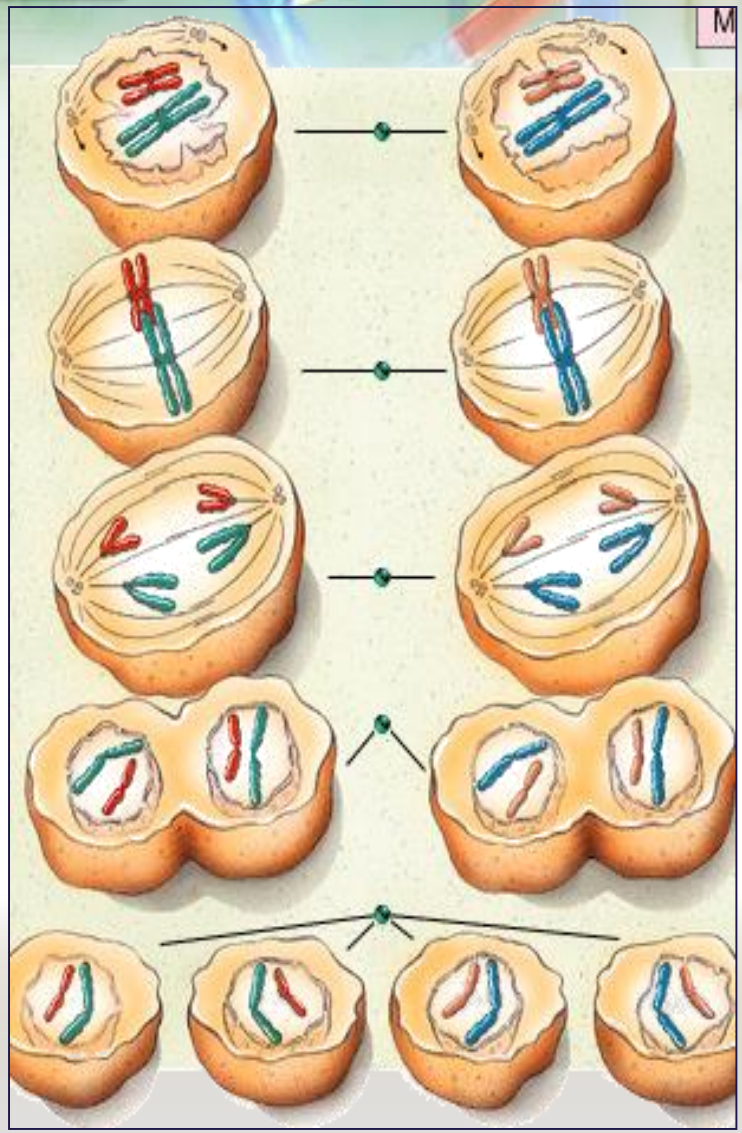
Stages of Mitosis & Meiosis

Mitosis



Meiosis



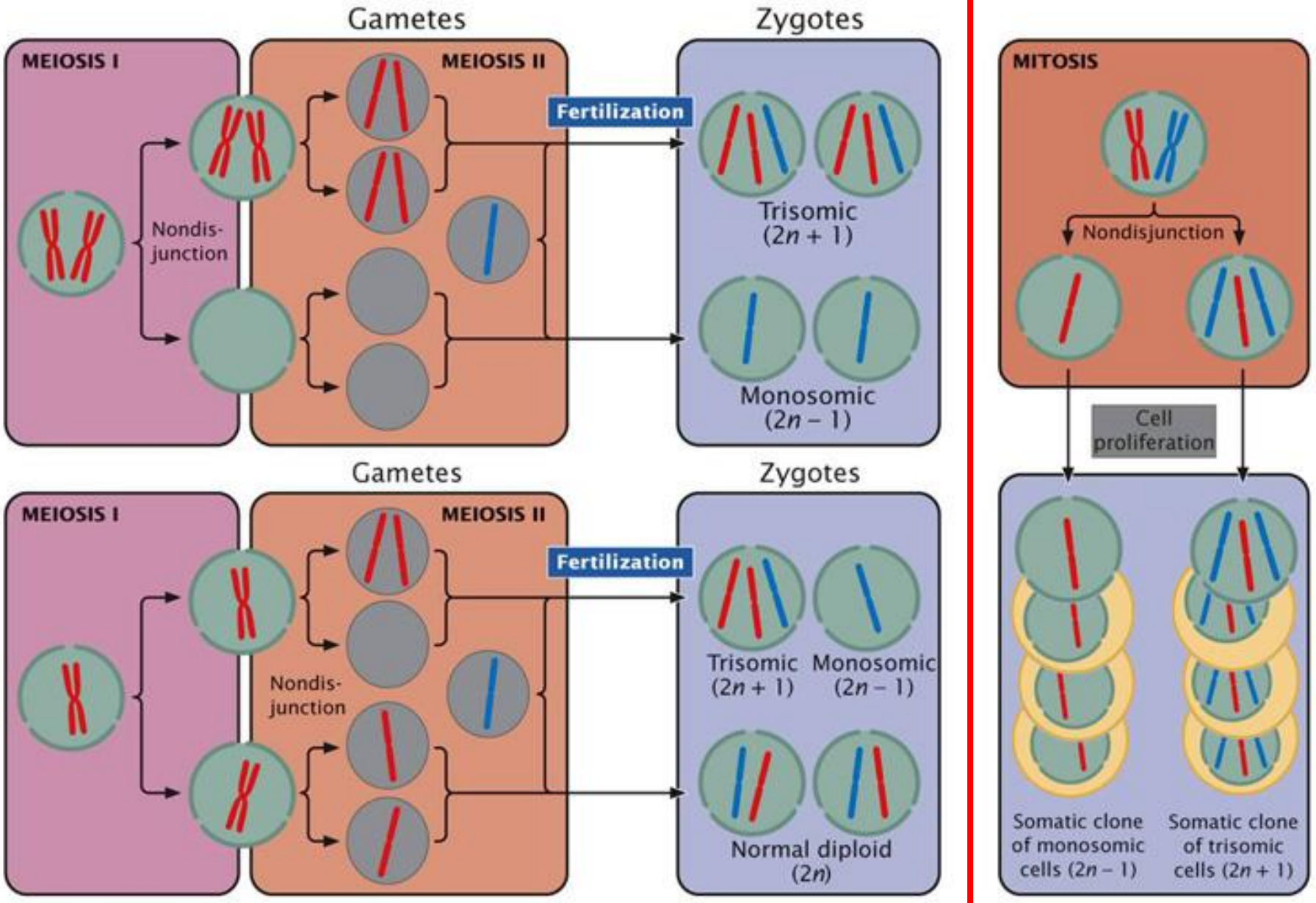


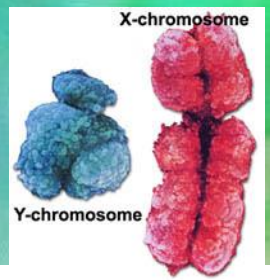
Nondisjunction in Meiosis

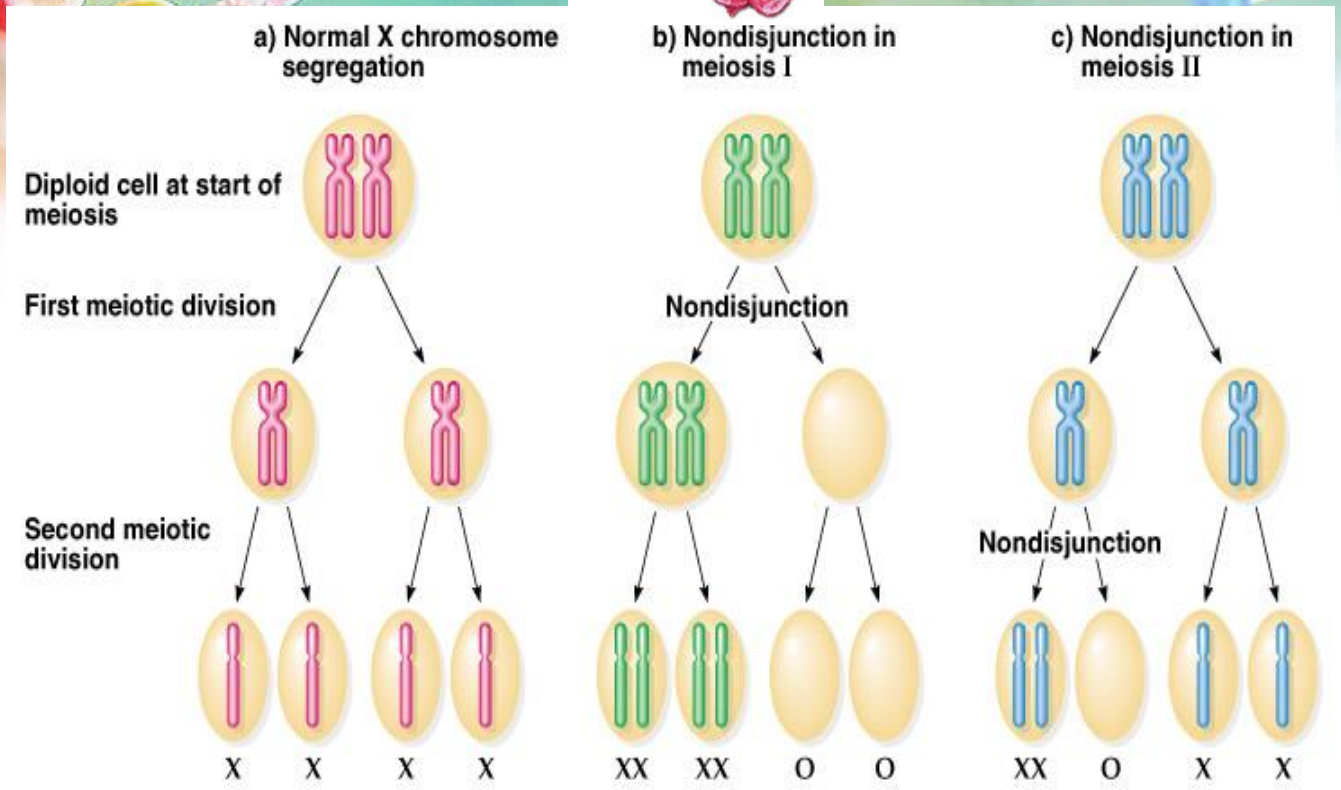
- Nondisjunction "not coming apart" is the failure of a chromosome pair to separate properly during meiosis 1, or of two chromatids of a chromosome to separate properly during meiosis 2 or mitosis.
- Can affect each pair of chromosomes
- Is not a rare event
- As a result, one daughter cell has two chromosomes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

MEIOSIS

MITOSIS







4 haploid gametes

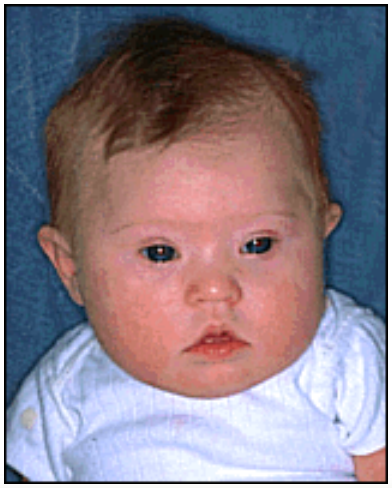
2 gametes with diploid number of X chromosome, and 2 gametes lacking X chromosome

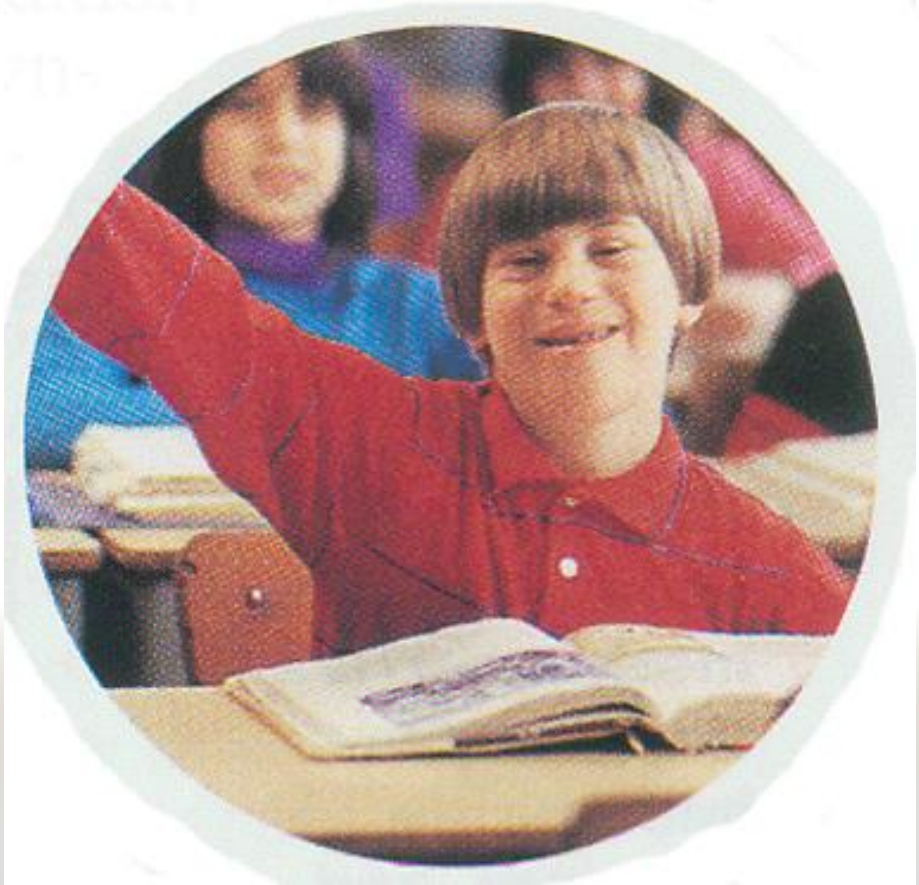
2 gametes with haploid number of X chromosome, 1 gamete with diploid number of X chromosome, and 1 gamete lacking X chromosome

Aneuploidy

- Autosomal:
  - Trisomy 21 (Down syndrome)
- Sex chromosome:
  - 47XXY (Klinefelter syndrome)
  - 45X (Turner syndrome)

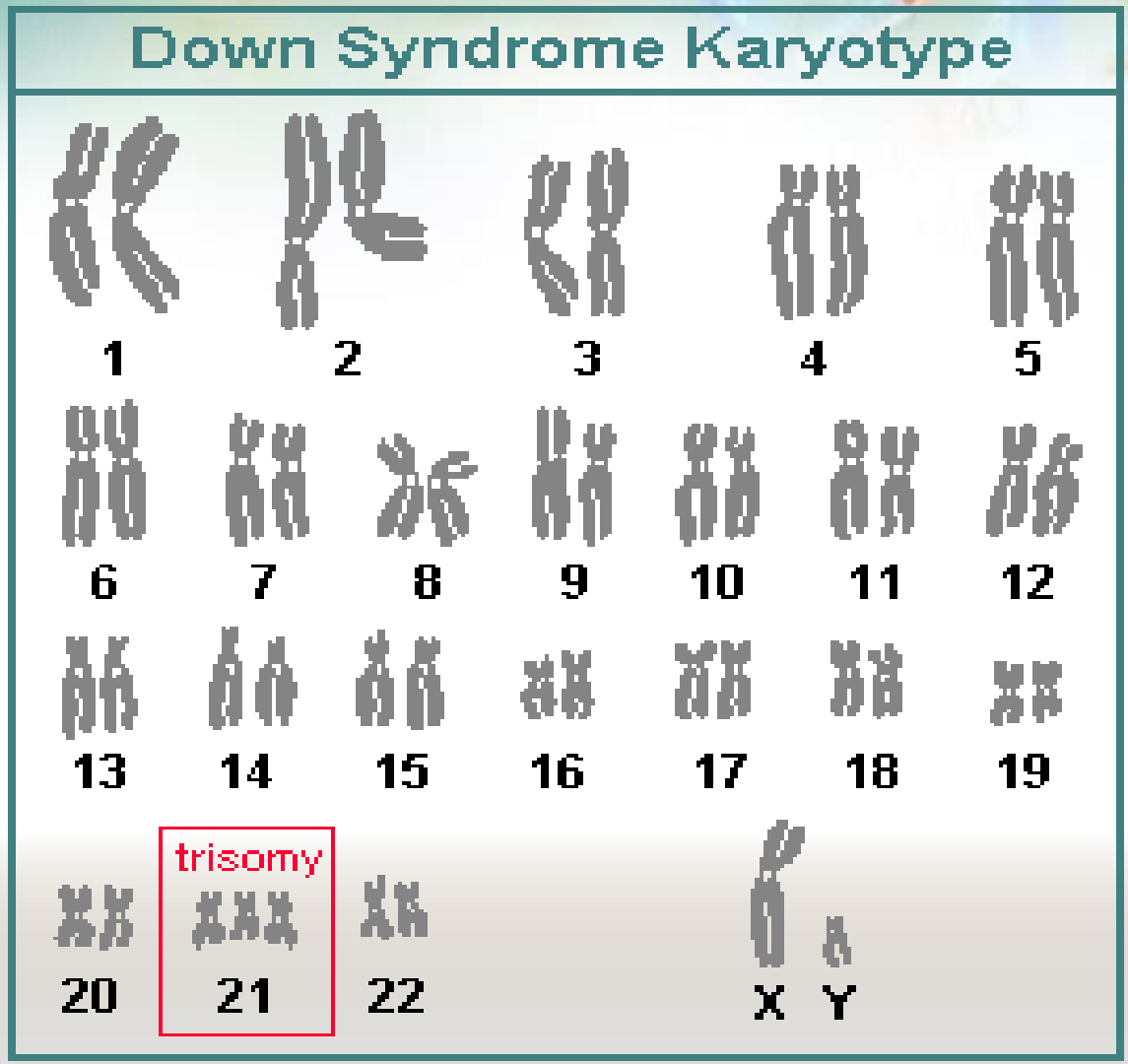
Down Syndrome



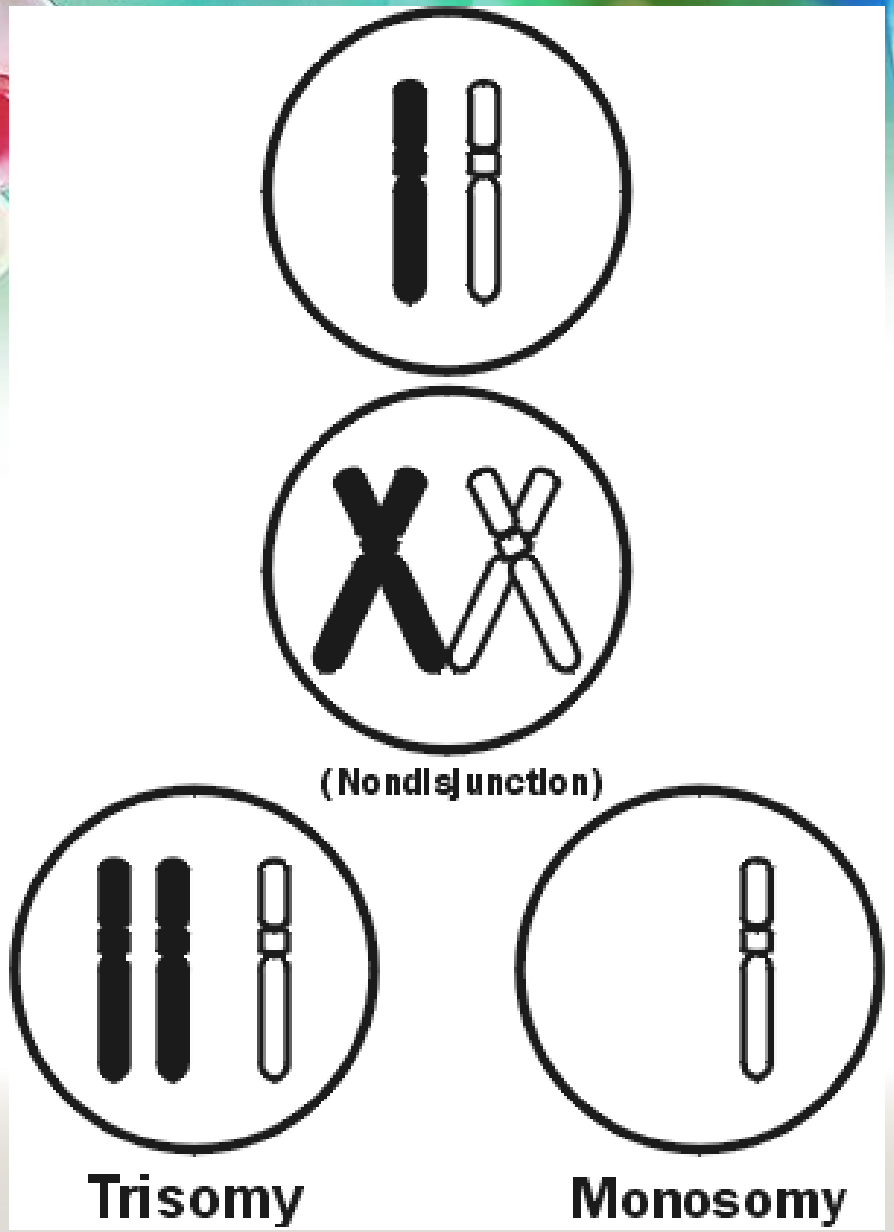


Down Syndrome

- Three copies of chromosome 21



3 copies
=
trisomy



1 copy =
monosomy

Down syndrome, trisomy 21

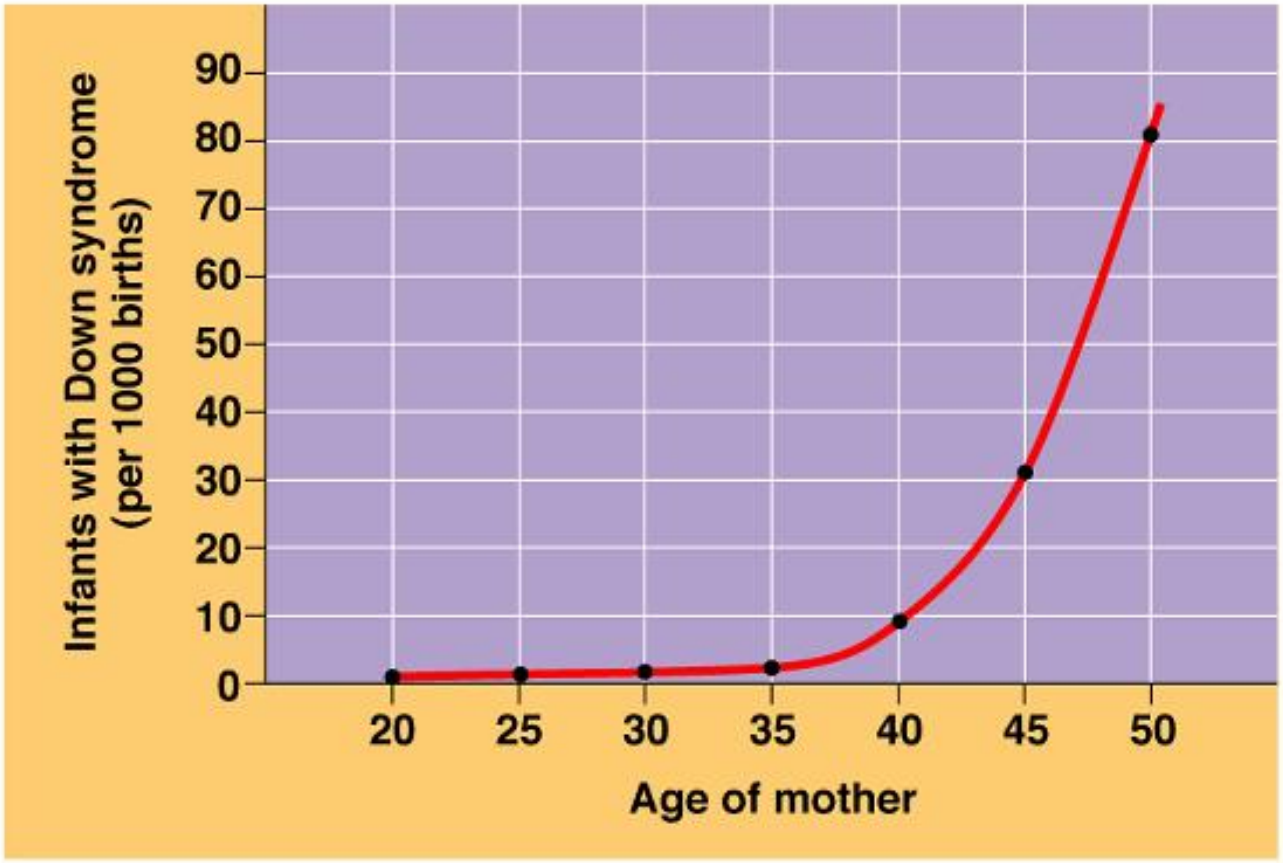
Karyotype: 47, XY, +21

- **Most cases arise from nondisjunction in the first meiotic division**
- **Mothers are the source of the extra chromosome in the majority of cases.**
- **The father contributing the extra chromosome in 15% of cases (i.e.** Down syndrome can also be the result of nondisjunction of the **father's** chromosome 21)
- **A small proportion of cases are mosaic and these probably arise from a nondisjunction event in an early zygotic division**

Features of Down Syndrome

- Low muscle tone
- Head and facial malformations: (Small round face, protruding tongue)
- Abnormalities of the extremities: (Short and broad hands, Stubby fingers)
- Developmental delays (mental retardation)
- Heart malformations
- Increased risk of infectious disease
- Rough skin
- Impotency in males
- Early death (Short lifespan)

Down Syndrome

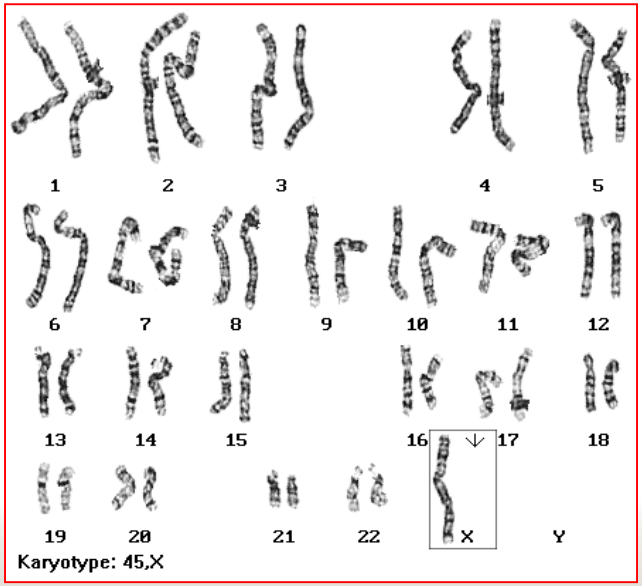


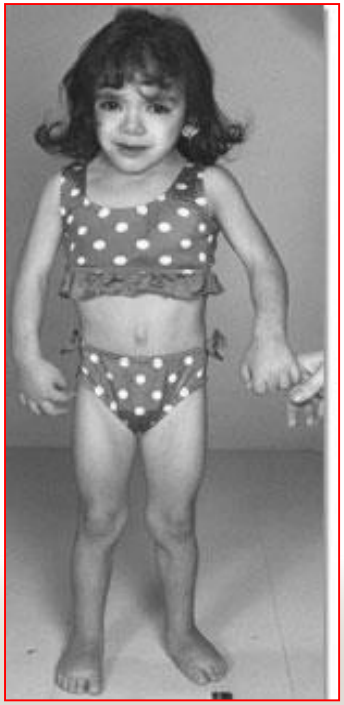
The incidence of trisomy 21 rises sharply with increasing maternal age

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





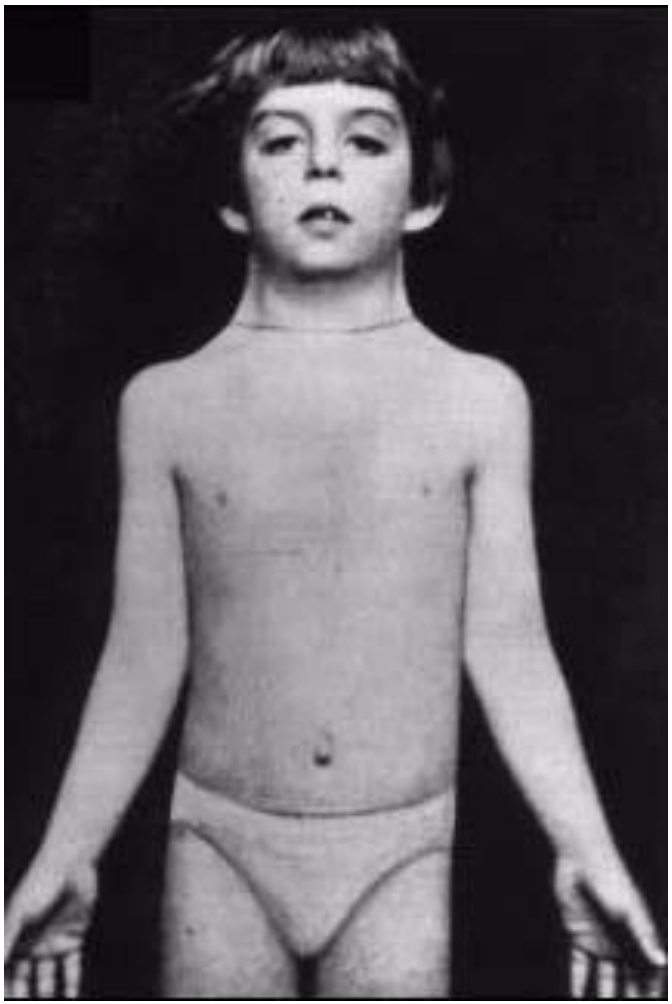
Turner Syndrome

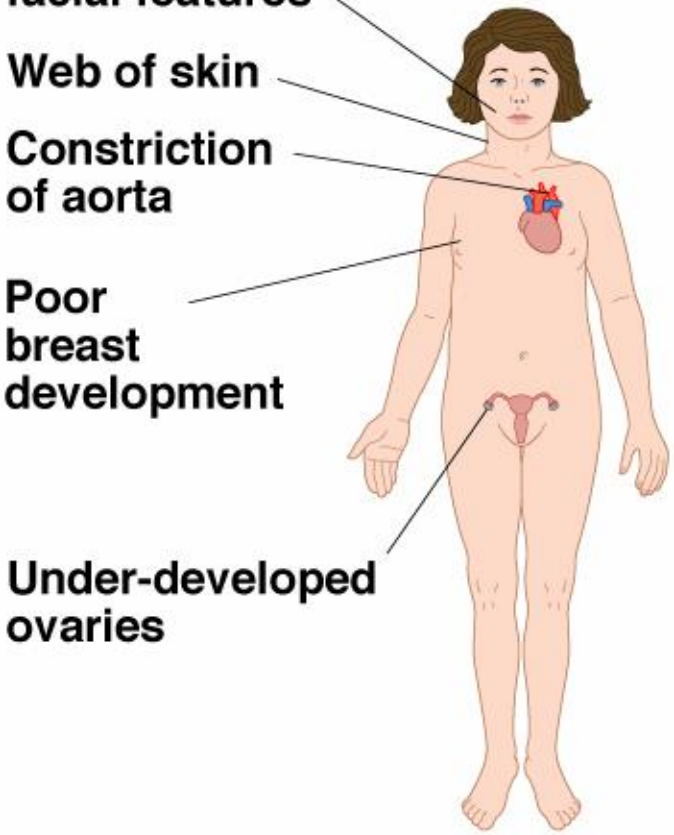
- Monosomy of sex chromosome: (Monosomy X: 45, XO) i.e. only one X chromosome is present.
- Occurrence – 1 in 2500 live female births
- The only viable monosomy in humans
- Individuals are genetically female, not mature sexually and sterile

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

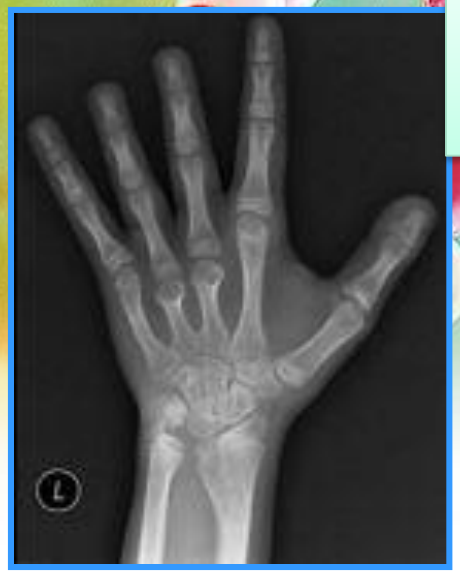




96-98% do not survive to birth

Features of Turner Syndrome,

Continued…



Cardiovascular

Bicuspid aortic valve

Coarctation of aorta

Thoracic aortic aneurysm (aortic root dilatation)

Skeletal

Short stature

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

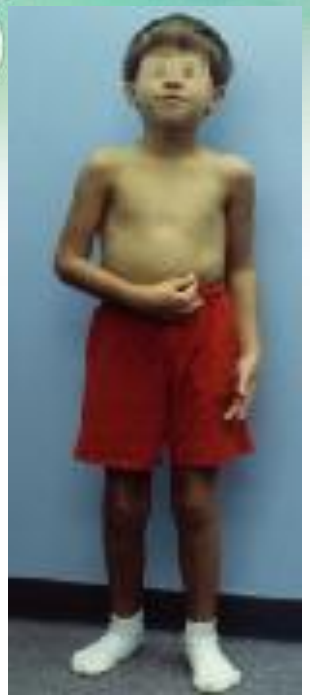
Osteoporosis (due to lack of estrogen)

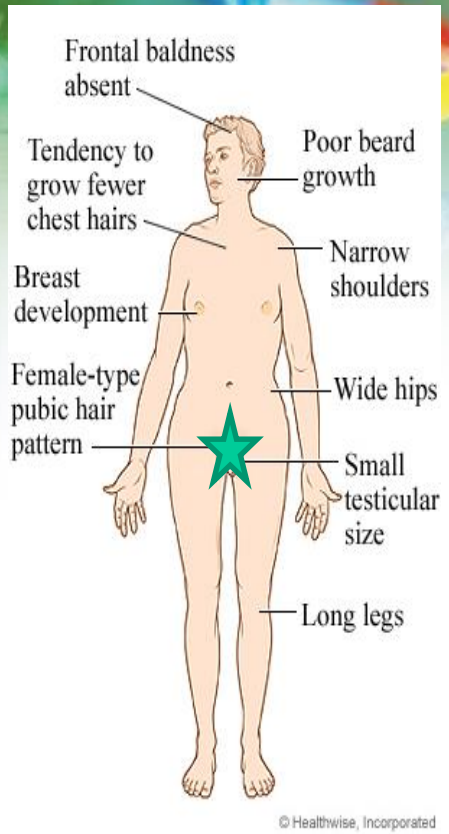
Scoliosis

Reproductive

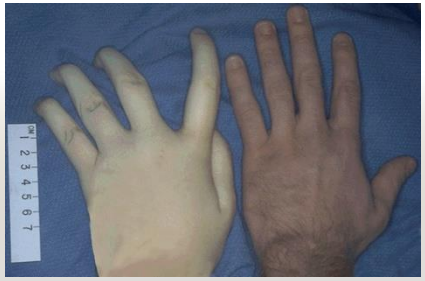
Women with Turner syndrome are almost universally infertile

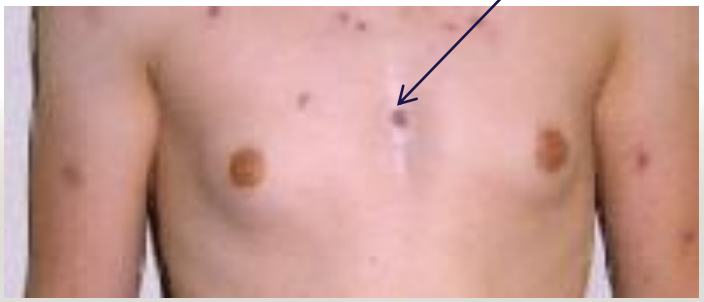
Klinefelter Syndrome





Brown spots (nevi)





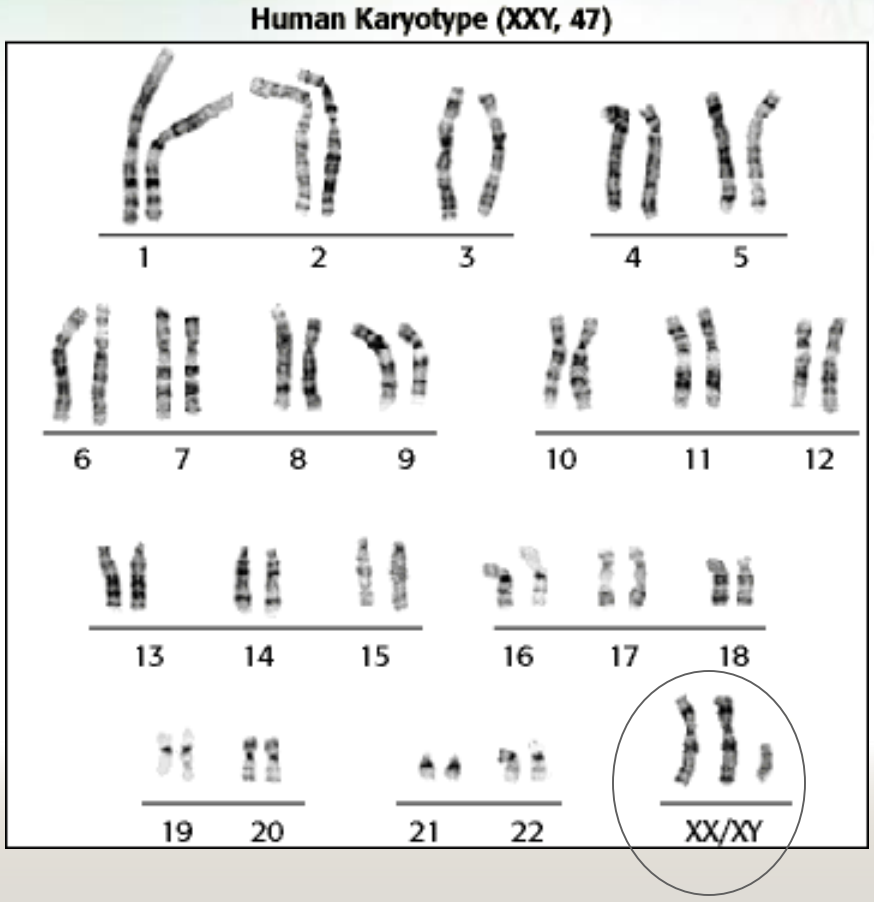
Klinefelter Syndrome

1 in 1,100 births

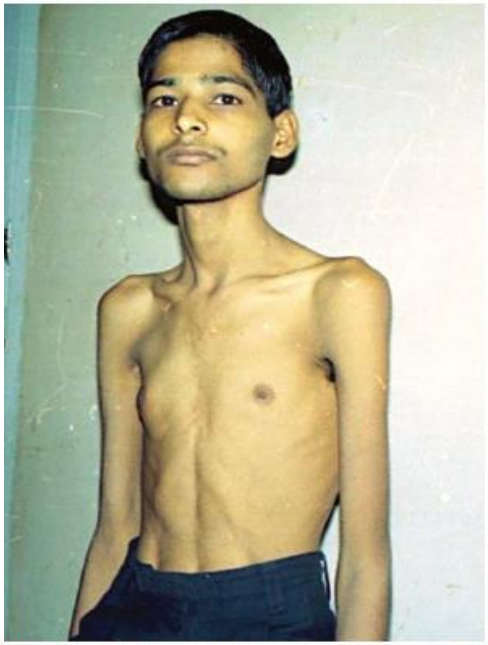
47 chromosomes

47, XXY

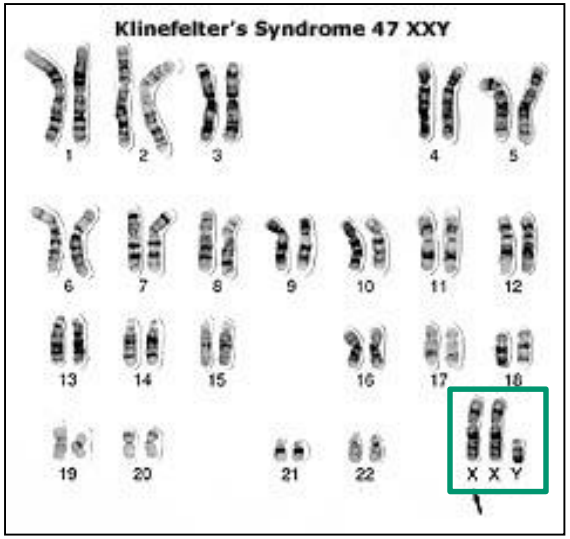
#23 Trisomy Nondisjunction



Klinefelter Syndrome: 47,XXY males



: Photograph showing development of gynecomastia in a old male after 2 months of isoniazid containing Category 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; Family history.

Triple test (measuring the alpha fetoprotein (AFP), human chorionic gonadotropin (hCG), and estriol): if positive it indicates an increased risk of having diseases due to chromosomal anomalies

- **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

- 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!