Klinefelter,Turner & Down Syndromes

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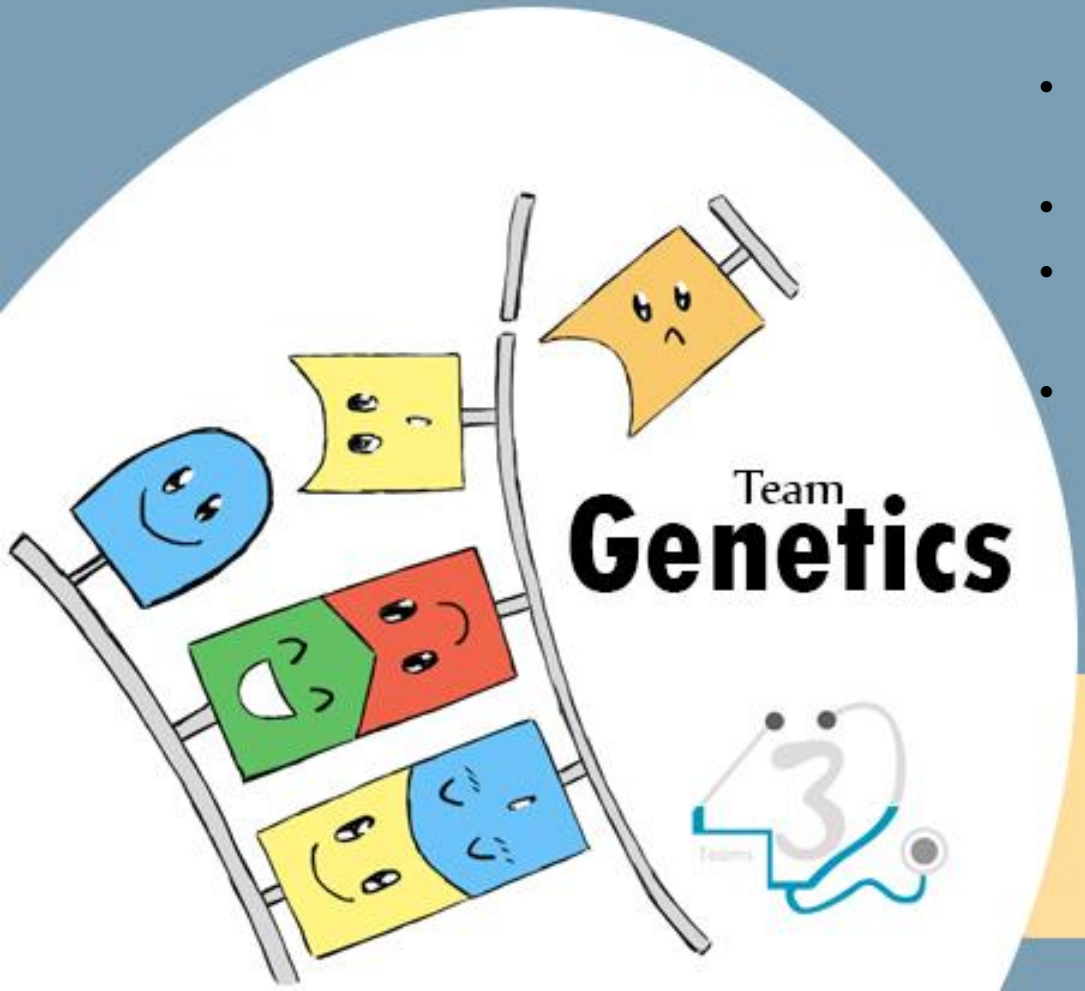
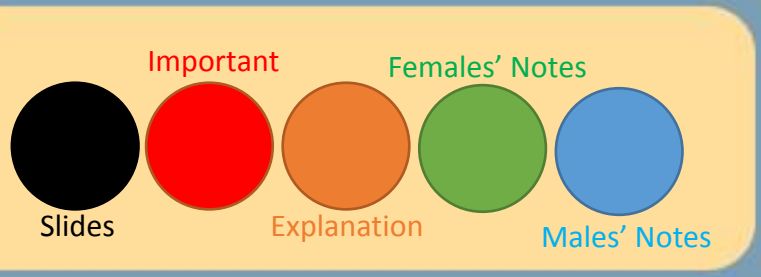


Lecture objective:

- Define non-disjunction and describe its consequences for meiosis and mitosis.
- Classify chromosomal abnormalities
- Understand the common numerical chromosomal disorders: mono and trisomy
- Understand the common numerical sex chromosome disorders: Turner`s & Klinefelter`s syndromes



Mind Map

Stages of Mitosis & Meiosis

- Non-disjunction
- Aneuploidy

Polyploidy

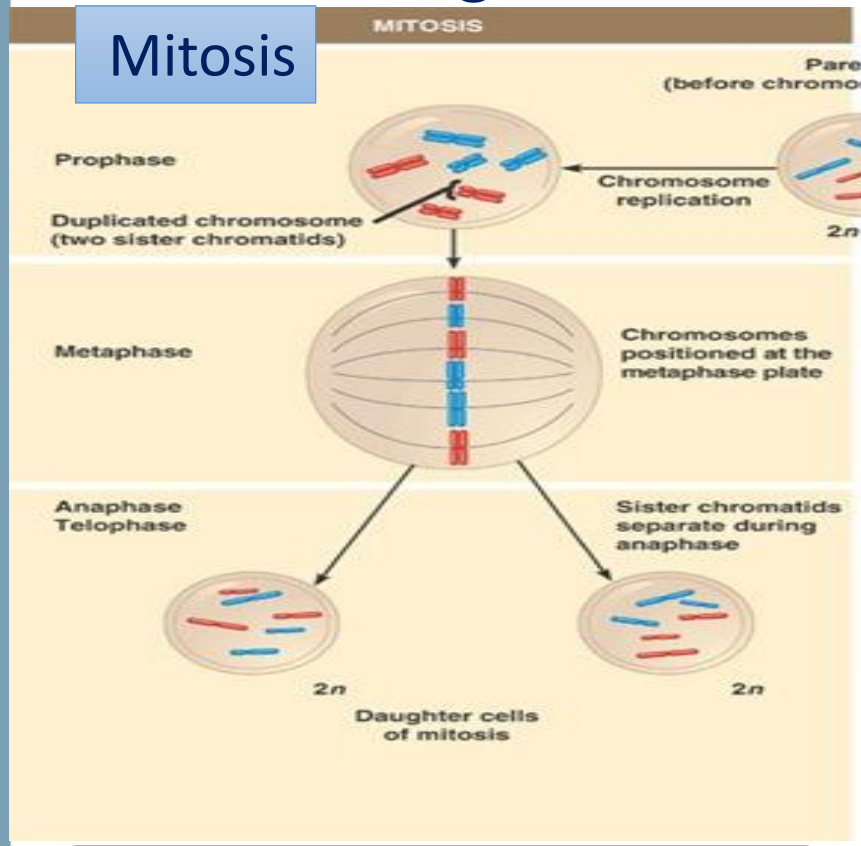
- Autosomal: Down syndrome
- Sex chromosomes: Turner & Klinefelter

Chromosomal tests

- FISH
- DNA & PCR

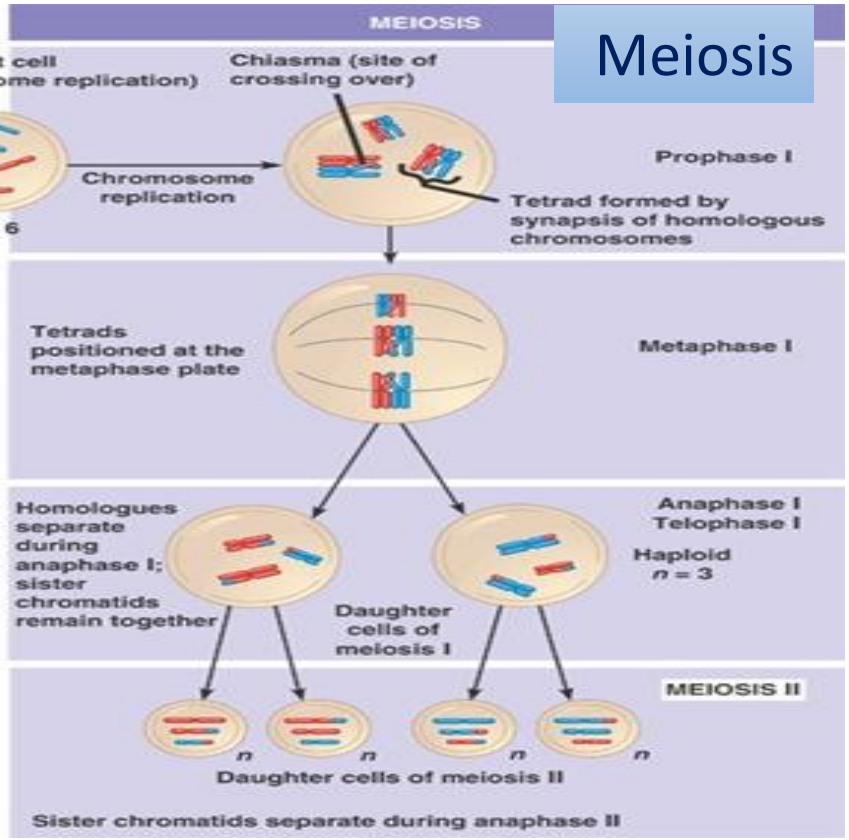
Stages of Mitosis & Meiosis

Mitosis



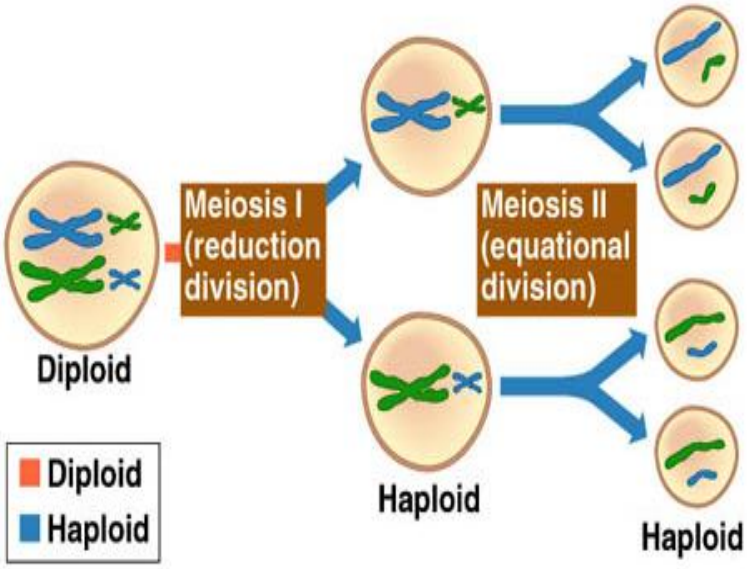
A process of asexual reproduction in which the cell divides in two producing a replica, with an equal number of chromosomes in each **diploid cell resulting**

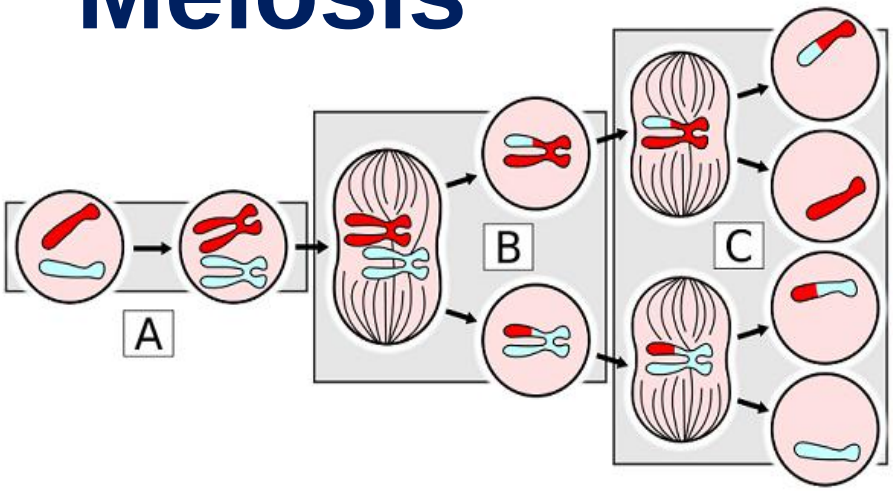
Meiosis



The process of cell division in sexually reproducing organisms that reduces the number of chromosomes in reproductive , **from diploid to haploidcells leading to the production of Gametes.**

Stages of Meiosis





Click here

There is useful video for the explanation of these stages

Non-disjunction in Meiosis

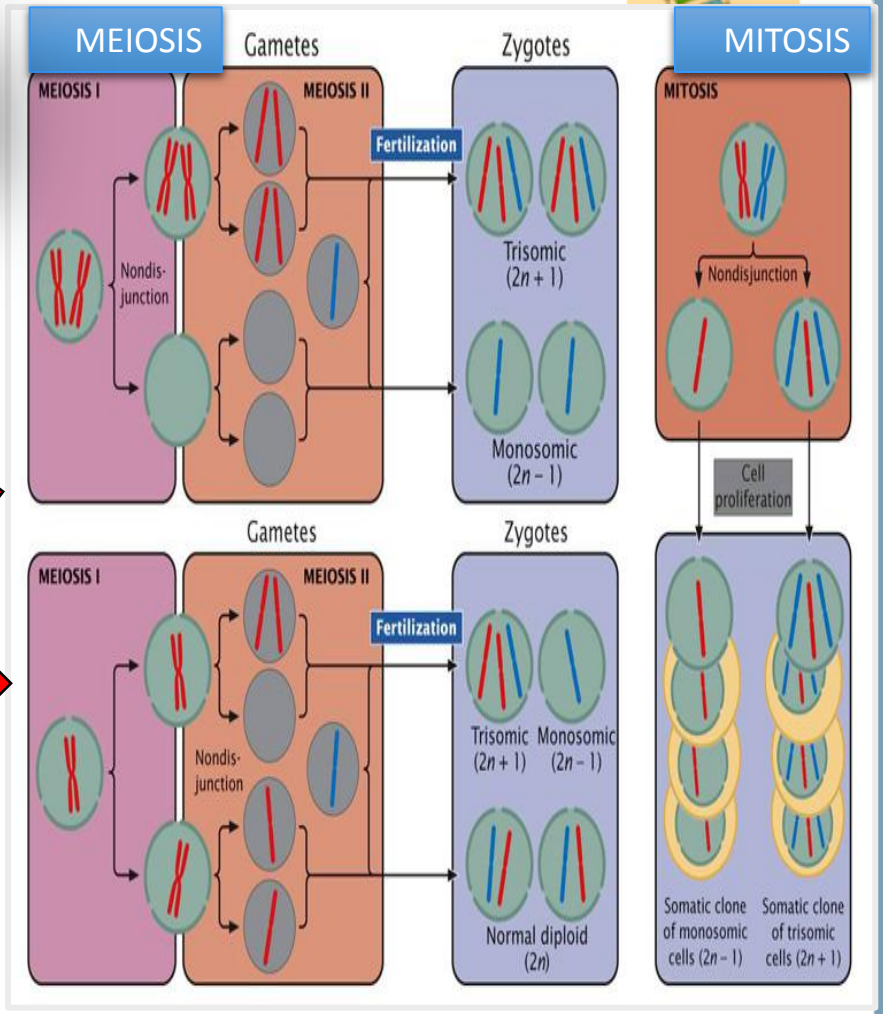
- Nondisjunction ("not coming apart") is the failure of chromosome pairs to separate properly during meiosis

stage 1

or

stage 2

- 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)



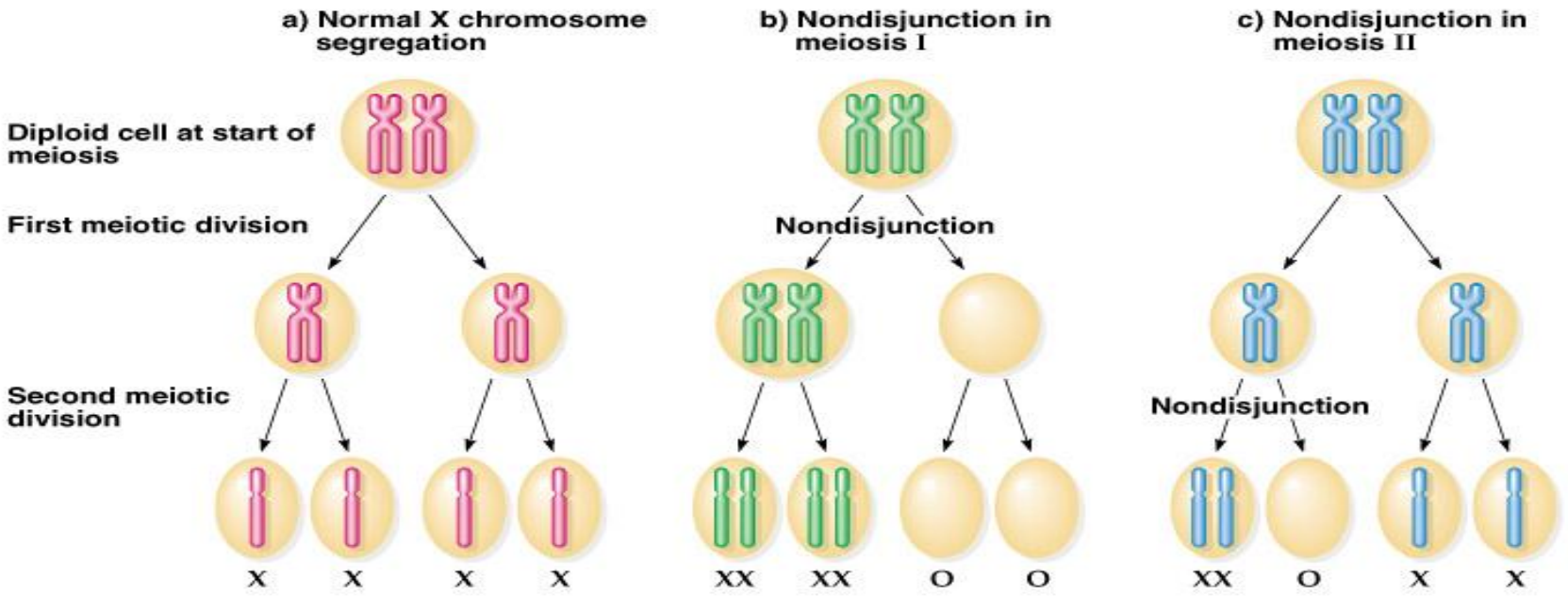
Autosomal

Trisomy 21 (Down syndrome)

Sex chromosome

-47XXY (Klinefelter syndrome)

- 45X (Turner syndrome)



For your information

Polyploidy When a cell contains more than two sets of chromosomes, polyploidy occurs. So it alters the chromosome number in a cell. Polyploidy can be seen frequently in flowering plants including important crop plants but rarely in animals, except vertebrates and invertebrates. Several types of polyploidy occur through several processes. Autopolyploidy is one type that is formed by multiplication of the genome of same species. Autopolyploidy is produced in sexual reproduction during meiosis by the non disjunction of homologous chromosomes in metaphase I or abnormal cell division in mitosis. Allopolyploidy occurs due to the combination of genomes of different species such as in hybrid species. Polyploidy also can be induced using various chemicals such as colchicine by inhibiting cell division.

Aneuploidy & Polyploidy

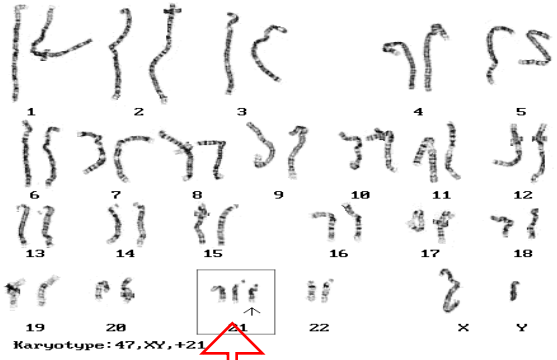
- **Aneuploidy refers to a numerical change in part of the chromosome set**
- **Polyploidy refers to a numerical change in the whole set of chromosomes:**

A. **Autosomal:**
   1. **Trisomy 21 (Down syndrome)**

B. **Sex chromosome:**
   1. **47XXY (Klinefelter syndrome)**
   2. **45X (Turner syndrome)**

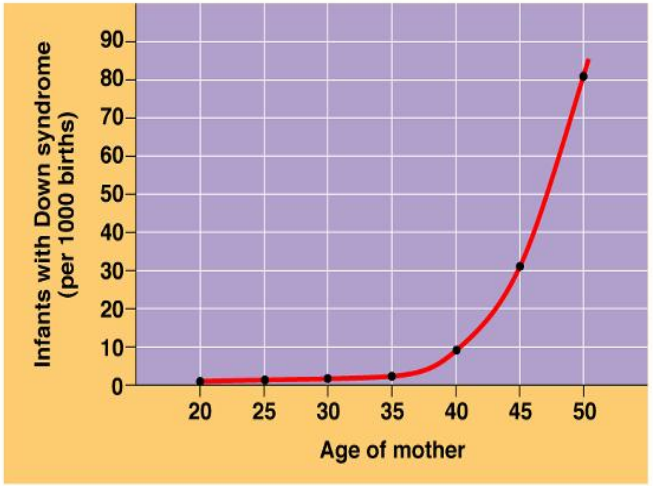
Polyploidy refers to a numerical change in a whole set of chromosomes. Organisms in which a particular chromosome, or chromosome segment, is under- or overrepresented are said to be aneuploid (from the Greek words meaning "not", "good", and "fold"). Therefore the distinction between aneuploidy and polyploidy is that aneuploidy refers to a numerical change in part of the chromosome set, whereas polyploidy refers to a numerical change in the whole set of chromosomes

A- Down syndrome
trisomy 21
Karyotype: 47, XY, +21



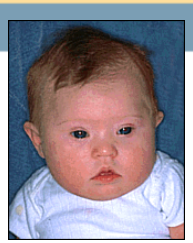
Three copies of chromosome 21

- **The incidence of trisomy 21 rises sharply with increasing maternal age**
- **Most cases arise from non disjunction in the first meiotic division**
- **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 non disjunction event in an early zygotic division**

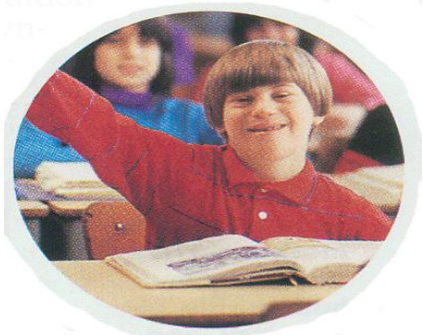


Mosaic Down syndrome In this rare form of Down syndrome, children have some cells with an extra copy of chromosome 21. This mosaic of normal and abnormal cells is caused by abnormal cell division after fertilization.

Features of Down syndrome

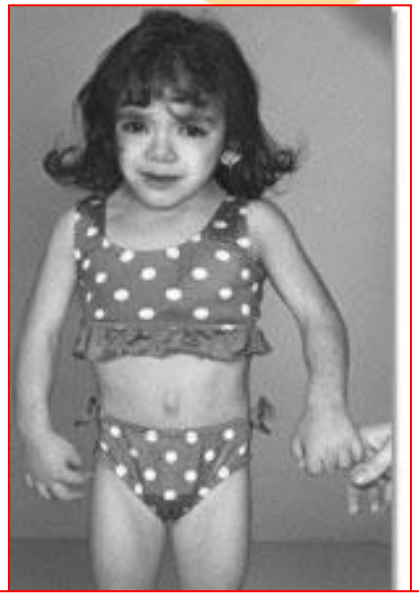


- ❖Short, broad hands
- ❖Stubby fingers
- ❖Rough skin
- ❖Impotency in males
- ❖Mentally retarded
- ❖Small round face
- ❖Protruding tongue
- ❖Short lifespan
- ❖Low muscle tone
- ❖Head and facial malformations
- ❖Abnormalities of the extremities
- ❖Developmental delays
- ❖Heart malformations
- ❖Increased risk of infectious disease
- ❖Early death



Features include low muscle tone, a tendency to keep mouth open with a protrusion of the tongue, head and facial malformations such as a short small head with upwardly slanting eyelid folds, a depressed nasal bridge, a small nose, misshapen ears, narrow roof of the mouth, dental abnormalities, excessive skin on the back of the neck, and a relatively flat facial profile. People with Down syndrome also have abnormalities of the extremities including unusually short arms, legs, and fingers, as well as unusual skin patterns. Affected individuals might also be short in stature, have poor coordination, developmental delays, as well as hearing impairment. (7) Sometimes Down syndrome can be associated with structural malformations of the heart at birth and an increased chance of infectious disease including leukemia. These problems can potentially be life-threatening. Early death is also associated with Down syndrome. (7)

B- Turner Syndrome (Monosomy X: 45, XO)



- **Monosomy of sex chromosome**

  (only one X chromosome present)

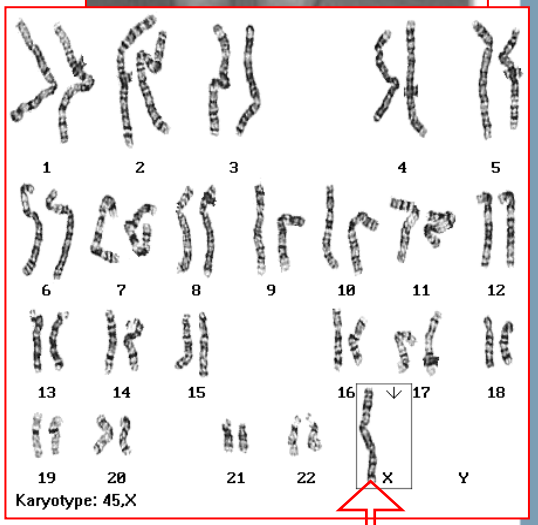
- **Occurring in 1 in 2500 phenotypic females**

  (Incidence is considered high)

- **The only viable monosomy in human**

- **Characteristics:**

- **Webbed neck**
- **not mature sexually**
- **Sterile**
- **Short stature**
- **Broad chest**
- **Low hairline**
- **Streak ovaries**
- **Normal intelligence**
- **Normal life span**
- **Individuals are genetically female**



Turner syndrome is normally found in woman and is caused by the absence or partial absence of an X chromosome. There is about one case of Turner syndrome in 2500 live female births. Approximately 60,000 girls and women are affected in the United States with around 800 new cases diagnosed every year. (8,9)

Features of Turner Syndrome

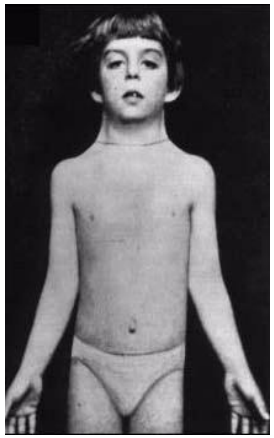
Cardiovascular	Skeletal	Reproductive	Other
cardiovascular constriction	Short fourth metacarpal/matatarsal bone may be unusually short (+/- short 3rd and 5th).	Lack of ovarian development	Short stature
Bicuspid aortic valve	Osteoporosis (due to lack of estrogen)	Women with Turner syndrome are almost universally infertile	Diabetes
Coarctation of the aorta	Scoliosis	96-98% do not survive to birth	Kidney and thyroid problem
Thoracic aortic aneurysm (aortic root dilatation			

Turner Syndrome

- **It is important to note that unlike Trisomy 13, Trisomy 18, and Down syndrome, developmental delays are not associated with Turner Syndrome**
- **Treatment:**

growth hormones, and estrogen replacement therapy.

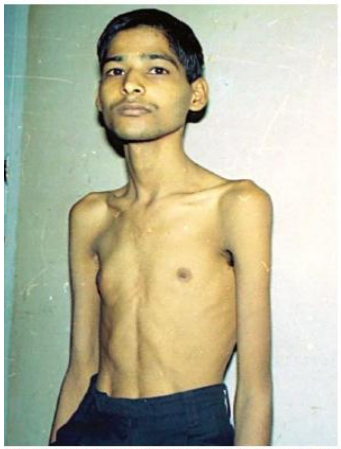
Additionally, reproductive technology can help women with Turner syndrome become pregnant



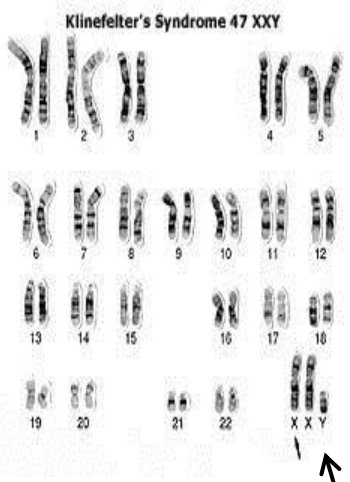
Short stature and lack of ovarian development are among the most common characteristics of Turner syndrome. Additionally, neck abnormalities including a webbed neck and low hairline can also occur. Skeletal disorders including scoliosis (curvature of the spine), dislocated hips, and elbows that turn out can also be characteristics. People with Turner syndrome are more likely to have certain health problems such as osteoporosis, cardiovascular problems including constriction of the aorta and high blood pressure, and diabetes. Kidney and thyroid problems result in about 1/3 of the cases. It is also important to note that unlike Trisomy 13, Trisomy 18, and Down syndrome, developmental delays are not associated with Turner Syndrome. In fact, there is no association between developmental delays and any sex chromosomal abnormality. This indicates that genes affecting mental development and ability lie only on autosomal chromosomes. Early death is also not associated with any of the sex linked chromosomal abnormalities. (8,9).
Turner syndrome is commonly treated with growth hormones, and estrogen replacement therapy. Additionally, reproductive technology can help women with Turner syndrome become pregnant. (4)

C- Klinefelter's Syndrome "Trisomy 47,XXY males"

- Incidence 1:1000 male "high"
- Male sex organs; unusually small testes which fail to produce normal levels of testosterone→ breast enlargement (gynaecomastia) and other feminine body characteristic



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



- Patients are taller and thinner than average may have a slight reduction in IQ but generally they have normal intelligence
- No spermatogenesis → sterile
- 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.

*23 Trisomy Nondisjunction

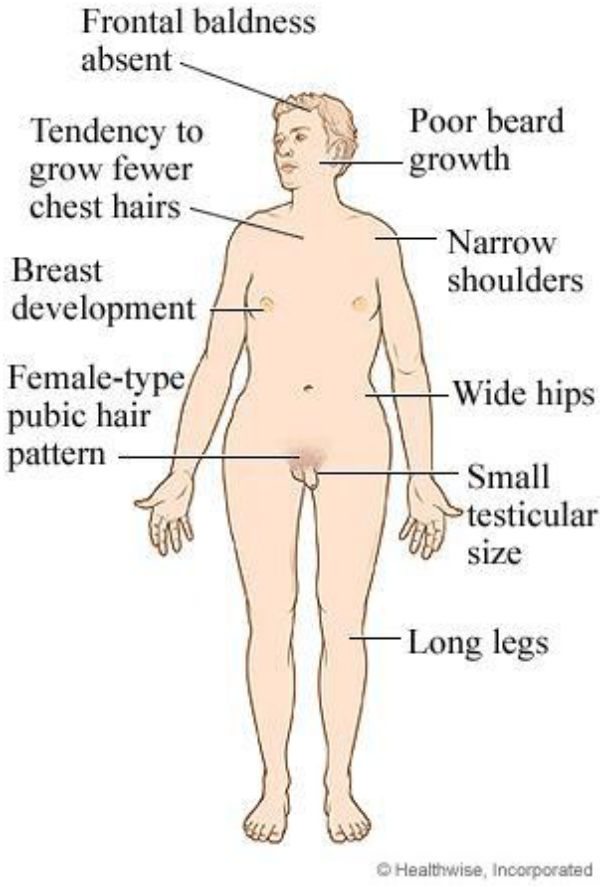
Features of Klinefelter's Syndrome

Longer fingers and arms	Longer fingers and arms
Scarce beard	Sterile(infertility)
Tall	Sparse facial and body hair
Developmental Delays	Normal lifespan
Brown spots (nevi)	↑ risk of breast cancer
Low mental ability	↑risk of autoimmune disorders
dental problems	depression
leg ulcers	osteoprosis
Delays in speech and motor skills	as deficits in attention, auditory processing and social skills
sexually underdeveloped, though in some case testicular function is preserved	

Treatment:
Testosterone therapy and assisted learning

Features of Klinefelter's Syndrome

- Characteristics normally associated with Klinefelter syndrome include being tall, sexually underdeveloped, and infertile, though in some case testicular function is preserved.
- Sparse facial and body hair is also a common characteristic.
- Klinefelter's can also cause delays in speech and motor skills as well as deficits in attention, auditory processing and social skills.
- Learning disabilities, anxiety, and depression can also result.
- Treatment for these problems includes testosterone therapy and assisted learning.
- Finally, people with Klinefelter's have an increased chance of certain health problems including autoimmune disorders such as type II diabetes, breast cancer, osteoporosis, leg ulcers, depression, and dental problems.



Sex chromosome unbalance "much less harmful"

47, XYY	XXX females
May be without any symptoms. Males are tall but normally proportioned. 10 - 15 points reduction in IQ compared to sibs.	It seems to do little harm, individuals are fertile and do not transmit the extra chromosome. They have Normal IQ comparable to that of Kleinfelter's males

For your knowledge:

- Not all chromosomal mutations are harmful.
- Polyploidy (extra sets of chromosomes) can produce stronger and larger plants.
- Important crop plants are produced this way, including bananas!

When to do a chromosomal test ?

❖Prenatal

maternal age>37yrs; USS changes; Family history

Triple test = increased risk

❖ postnatal:

Learning & developmental disability; growth retardation

❖ Infertility

Recurrent miscarriage, primary infertility

How Do we know there is chromosome abnormality?

1- Rapid Aneuploidy Screening by FISH (Fluorescence InSitu Hybridization)
(FISH) is a test that "maps" the genetic material in a persons cells. This test can be used to visualize specific genes or portions of genes a person's cells
Available on amniocentesis sample
Uncultured amniocytes
FISH probes for X,Y, 21
Result in 24-48 hours
Proceed onto full karyotype (11-14 days)

2- New techniques	
qf (quantitative) PCR	Fetal DNA
able to measure number of copies of a chromosome . used for trisomy screening	at 6-8 weeks to determine sex look for presence of Y chromosome material

Male's Doctor Notes

- Down, Turner's and Klinefelter's Syndromes are the most prevalent genetic syndromes.
- They are chromosomal abnormalitis due to non-disjunction of the chromosomes.
- All the body cells are diploid except the gonads which are haploid.
- If the non-disjunction occur in Stage 1= 100% abnormality , in Stage 2= 50% abnormality
- In the mitosis and meiosis, the chromosomes duplicate in a line called "metaphase plate".
- Abnormal disjunction occur either in Stage 1 or 2
- Aneuploidy means "imbalance"
- The no. of genes in the body almost : 20000-25000 genes.
- Down's syndrome is an autosomal chromosomal abnormality.
- In Down's syndrome, the risk is proportional increased with the age of the pregnant women (especially over 35 years old)
- In turner's syndrome, 96-98% of babies do not survive at birth.

summary

A- Down syndrome	B- Turner's Syndrome	C- Klinefelter's Syndrome
1) trisomy 21 2) Karyotype: 47, XY, +21 3) Most cases arise from non disjunction in the first meiotic division 4) Features: • Mentally retarded • Short lifespan • Impotency in males	1) Monosomy of sex chromosome (only one X chromosome present) 2) genetically female 3) The only viable monosomy in humans **4) Features:** A. Webbed neck B. Normal intelligence C. Normal life span D. Increased risk of E. osteoporosis, cardiovascular constriction F. Women are almost G. universally infertile **5) treatment:** growth hormones, and estrogen replacement therapy.	1) 23 Trisomy Nondisjunction 2) 47,XXY 3) No spermatogenesis -> sterile 4) Features: A. Gynaecomastia B. Normal lifespan C. Tall 5) testosterone therapy and assisted learning

QUESTIONS

1- Which one of the following is not a Feature of Turner Syndrome:

A-Sterile

B-Short stature

C-Broad chest

D- abnormal life span

2- which one of the following syndromes is Monosomy:

A-Down syndrome

B-Turner's Syndrome

C-Klinefelter's Syndrome

3- Patient has breast enlargement and is sterile , which on of these syndromes does he has and what is the treatment ?

A. Down syndrome, health care

B. Turner's Syndrome, growth hormone

C. Klinefelter's Syndrome, testosterone

QUESTIONS

4- The patient come to you with Webbed neck, not mature sexually, Sterile, Short stature, Broad chest,Normal intelligence , which on of these syndromes does he has:

A. Down syndrome

B. Turner's Syndrome

C. Klinefelter's Syndrome

5- Most cases of down syndrome arise from :

A. non disjunction in the first meiotic division

B. disjunction in the first meiotic division

C. non disjunction in the second meiotic division

D. non disjunction in the first mitotic division

Q.	Ans.
1	D
2	B
3	C
4	B
5	A

For any questions, suggestions or problems, please contact us:

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GOOD LUCK

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