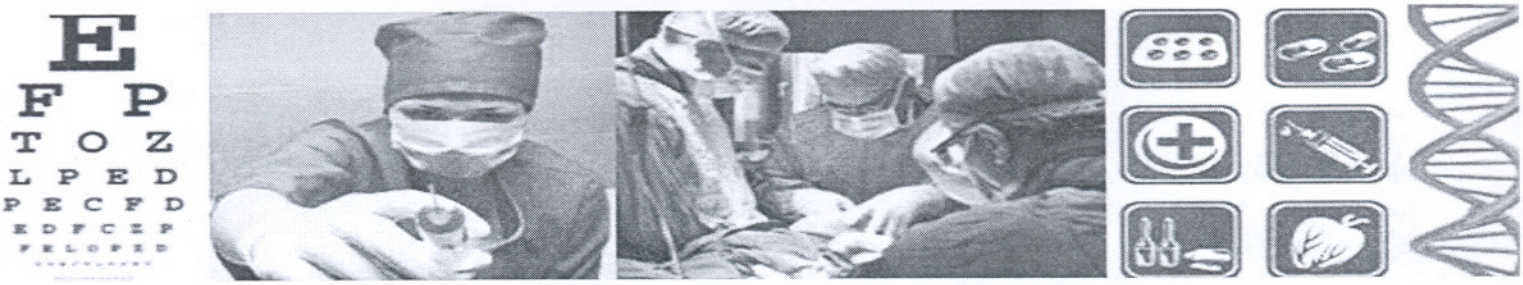
Foundation Block

كلية الطب البشري
السنة الأولى
1431_1432

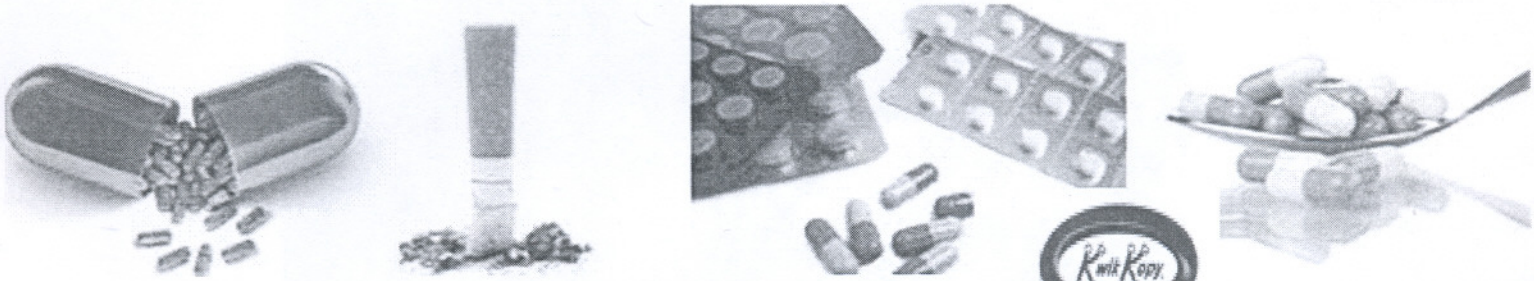
رقم المذكرة
60

عدد الصفحات
21

TEL : 014801989



Genetic
Chromosome anomalies
Lecture 2



- **LECTURE 2** CHROMOSOME ANOMALIES

A chromosome anomaly can be:

HOMOGENEOUS: when all the cells (studied) carry the anomaly.

MOSAIC: When only some cells carry the anomaly whilst others are normal (or carry another anomaly).

NUMERICAL: If there is one (or more) chromosome(s) in excess (trisomy) or missing (monosomy)

STRUCTURAL: If structural changes occur within the chromosomes themselves

A- numerical abnormalities

aneuploidy

Aneuploidy is the category of chromosome changes which do not involve whole sets. It is usually the consequence of a failure of a single chromosome (or bivalent) to complete division.

meiotic non-disjunction

Autosomes

- non disjunction in first meiotic division produces 4 unbalanced gametes.
- non disjunction in second division produces 2 unbalanced and 2 normal gametes

monosomies

Down syndrome, trisomy 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. A small proportion of cases are mosaic and these probably arise from a non disjunction event in an early zygotic division. About 4% of cases arise by inheritance of a translocation chromosome from a parent who is a balanced carrier. The symptoms include characteristic facial dysmorphologies, and an IQ of less than 50. Down syndrome is responsible for about 1/3 of all cases of moderate to severe mental handicap.

Trisomy 13

The incidence is about 1 in 5000 live births. 50% of these babies die within the first month and very few survive beyond the first year. There are multiple dysmorphic features. Most cases, as in Down's syndrome, involve maternal non-disjunction. Again, a significant fraction have a parent who is a translocation carrier.

Trisomy 18 (Edward's syndrome)

Incidence ~1 in 3000. Again most babies die in the first year and many within the first month.

Turner syndrome, 45, X

The incidence is about 1 in 500 female births but this is only the tip of the iceberg, 99% of Turner syndrome embryos are spontaneously aborted. Individuals are very short, they are usually infertile. Characteristic body shape changes include a broad chest with widely spaced nipples and may include a webbed neck. IQ and lifespan are unaffected.

Kleinfelter's syndrome, 47, XXY

The incidence at birth is about 1 in 1000 males. Testes are small and fail to produce normal levels of testosterone which leads to breast growth (gynaecomastia) in about 40% of cases and to poorly developed secondary sexual characteristics. There is no spermatogenesis. These males are taller and thinner than average and may have a slight reduction in IQ. Very rarely more extreme forms of Kleinfelter's syndrome occur where the patient has 48, XXXY or even 49, XXXXY karyotype. These individuals are generally severely retarded.

47, XYY

Incidence 1 in 1000 male births. May be without any symptoms. Males are tall but normally proportioned. 10 - 15 points reduction in IQ compared to sibs? More common in high security institutions than chance would suggest? Strangely, although they are fertile they do not seem to transmit the either this condition or Kleinfelter's syndrome.

XXX females

About one woman in 1000 has an extra X chromosome. 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 Kleinfelter's males.

euploidy

Euploidy is the category of chromosome changes which involve the addition or loss of complete sets of chromosomes.

triploidy

The possession of one complete extra set of chromosomes is usually caused by polyspermy, the fertilisation of an egg by more than one sperm. Such embryos will usually spontaneously abort.

tetraploidy

This is usually the result of a failure of the first zygotic division. It is also lethal to the embryo. Any other cell division may also fail to complete properly and in consequence a very small proportion of tetraploid cells can sometimes be found in normal individuals.

B- STRUCTURAL ANOMALIES

chromosomes can appear to break, and broken ends can rejoin in various ways:

- either as they were: restitution
- or, in case of 2 (or more) breaks, with interactive re-joining to make a structural aberration

- **Reciprocal translocation** A mutual exchange between terminal segments from the arms of 2 chromosomes

- **Robertsonian translocation** Fusion of 2 acrocentrics very close to the centromeres

- **Deletion** Loss of a segment, either interstitial or terminal, from a chromosome

- **Ring** A centric ring involves the deletion (often small) of the ends of both arms (including the telomeres) and rejoining of the median segment to itself in a circular structure.

- **Inversion** Inversion occurs when a segment of chromosome breaks, and rejoining within the chromosome effectively inverts it.

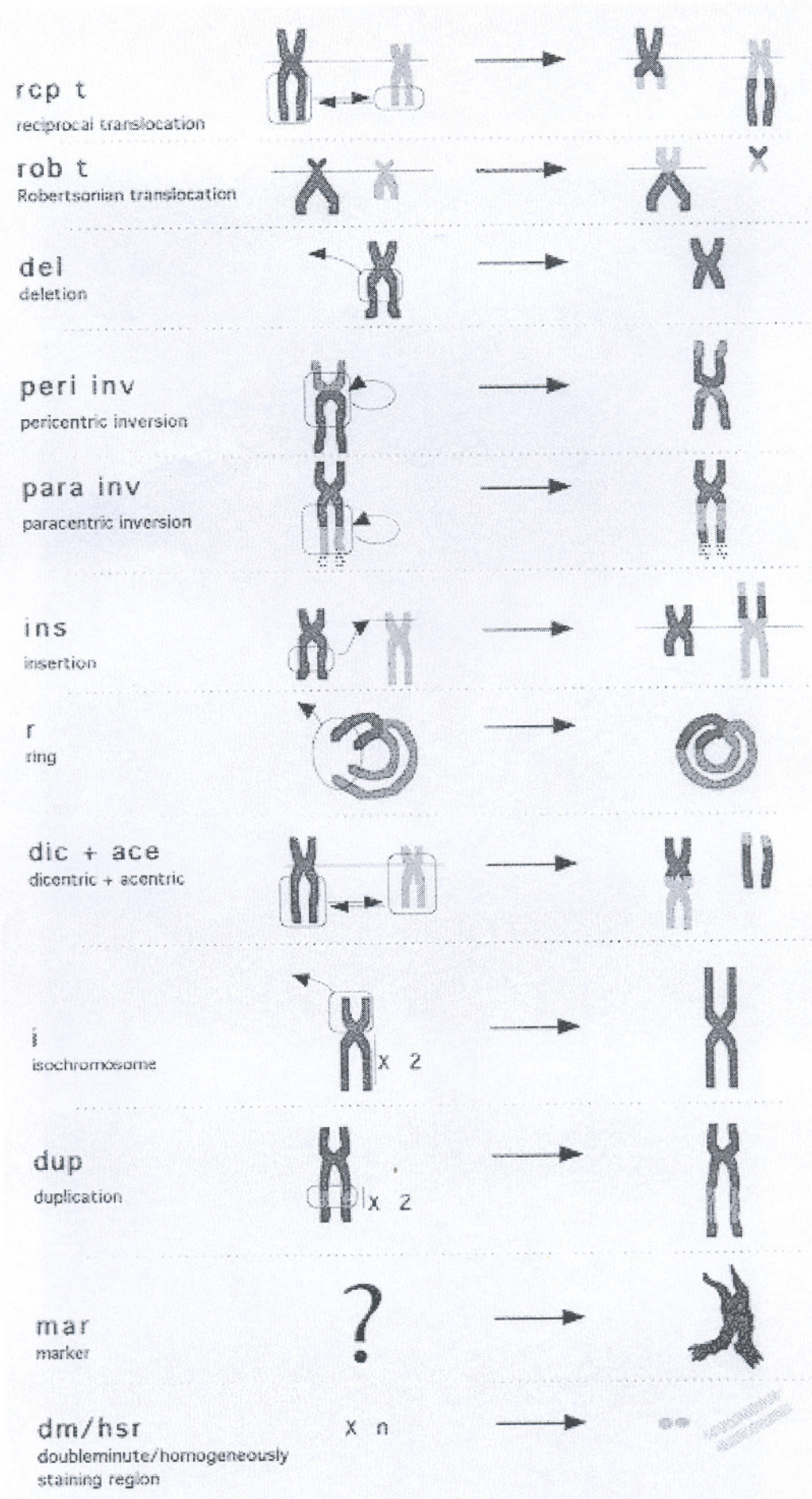
- An inversion is termed paracentric when the segment involved lies wholly within one chromosome arm.

- An inversion is said pericentric when the two break-points involved are sited on opposite sides of the centromere, and rejoining effectively inverts the central centromere-bearing segment.

- **Isochromosome** Loss of a complete arm, "replaced" by the duplication of the other arm

- **Duplication** A segment of chromosome is repeated, once or several times, the duplicated segment keeping the same orientation with respect to the centromere

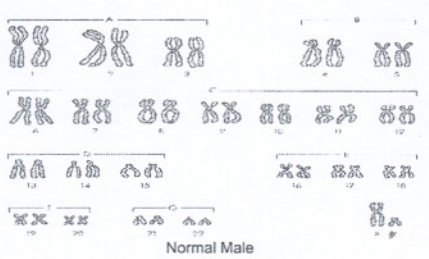
- **Dicentric** A chromosome with 2 centromeres



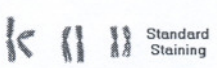
STRUCTURAL ANOMALIES

Medical Genetics

•LECTURE 2
CHROMOSOME ANOMALIES



Normal Male



Standard Staining

G-banded

Numerical Abnormalities

Polyploidy	Aneuploidy
Triploidies	Autosomal Trisomy (21, 13, 18)
Tetraploidy	Sex chromosomal - Monosomy (45,X) - 47,XXY. -47,XXX

Structural Abnormalities

- Translocation (t)
- Inversion
- Deletion (del)

CHROMOSOME ANOMALIES

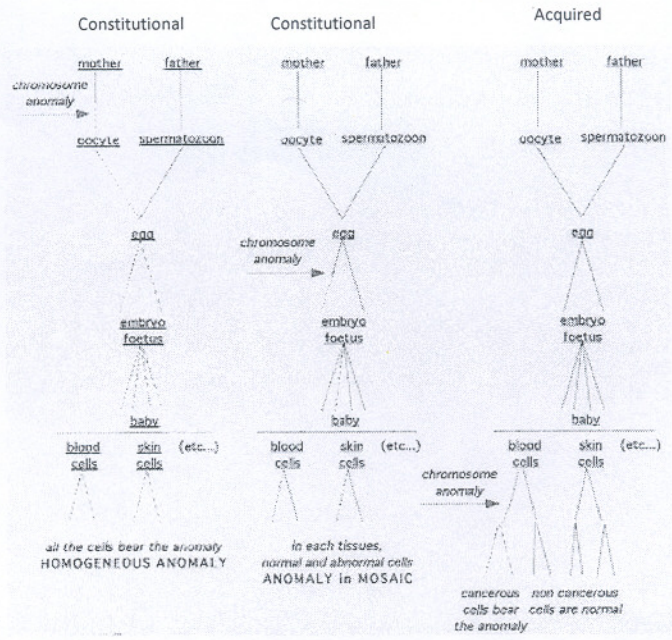
-TYPES
- MECHANISMS
- EFFECT
- TRANSMISSION
- FREQUENCES
- NUMENCLATURE

Consultant:Dr,Ghassan.Zidan

TYPES OF CHROMOSOME ANOMALIES

A chromosome anomaly can be:

-Numerical
-Structural
- Mosaic
-Constitutional
-Homogeneous
-Balanced



Consultant:Dr,Ghassan.Zidan

CLASSIFICATION OF CHROMOSOMAL ABNORMALITIES

Numerical Abnormalities

Structural Abnormalities

Polyploidy

Triploidies
Tetraploidy

Aneuploidy

Autosomal

Trisomy
(21, 13, 18)

Sex chromosomal

- Monosomy (45,X)
- 47,XXY.
- 47,XXX
- 48,XXXX
-49,XXXXY.

Gross

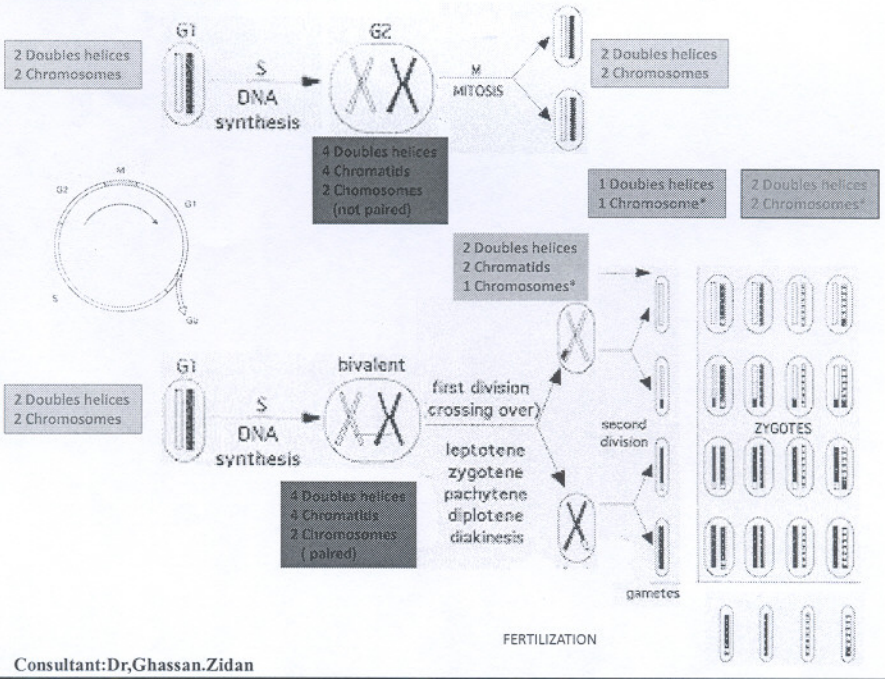
- Translocation (t)
- Inversion
- Deletion (del)

Microdeletion

- DG Syn22q11.2 del
- PWS 15q11-13 del
- AS 15q11-13 del
- WHS4P16.3 del
- MDS17q21.1 del

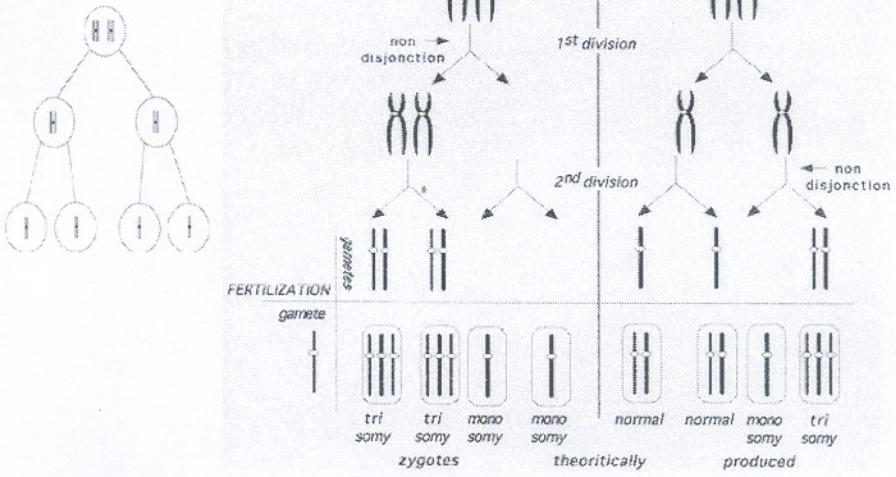
Consultant:Dr,Ghassan.Zidan

MITOSIS / MEIOSIS (Reminder) : **(Cyclic Quantitative Changes in DNA Content)**



Consultant:Dr,Ghassan.Zidan

Constitutional Homogeneous Numerical Abnormalities
(MECHANISMS OF FORMTION)
(Autosomes & XX)

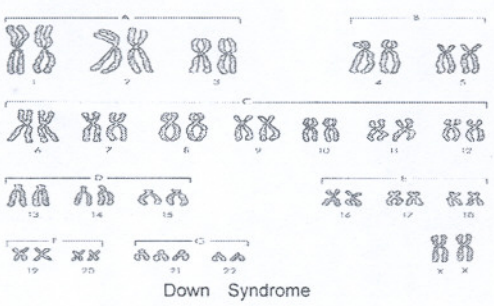


Meiotic non-disjunction

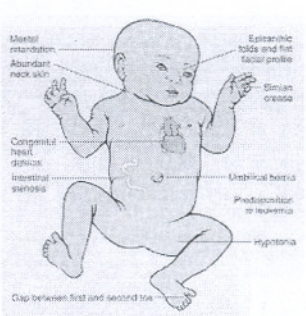
- can affect each pair of chromosomes
- is not a rare event,

- non disjunction in first meiotic division produces 4 unbalanced gametes.
- non disjunction in second division produces 2 unbalanced and 2 normal gametes.

- Gametes with an extra autosome
- Nullosomic gametes (missing one chromosome).



Down Syndrome



Down syndrome, trisomy 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.
A small proportion of cases are mosaic and these probably arise from a non disjunction event in an early zygotic division.
About 4% of cases arise by inheritance of a translocation chromosome from a parent who is a balanced carrier.
The symptoms include characteristic facial dysmorphologies, and an IQ of less than 50.
Down syndrome is responsible for about 1/3 of all cases of moderate to severe mental handicap.

Consultant:Dr,Ghassan.Zidan

Trisomy 13

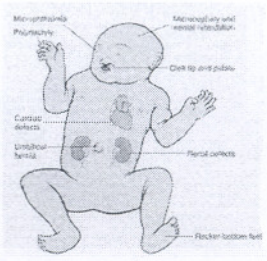
The incidence is about 1 in 5000 live births.

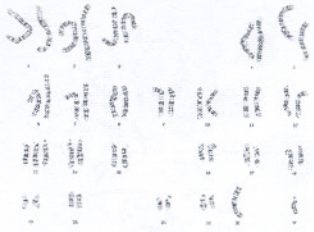
50% of these babies die within the first month and very few survive beyond the first year.

There are multiple dysmorphic features.

Most cases, as in Down's syndrome, involve maternal non-disjunction.

Again, a significant fraction have a parent who is a translocation carrier.

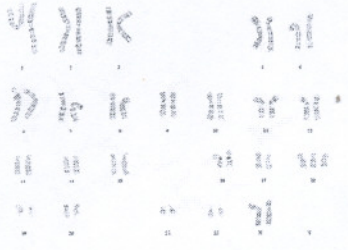


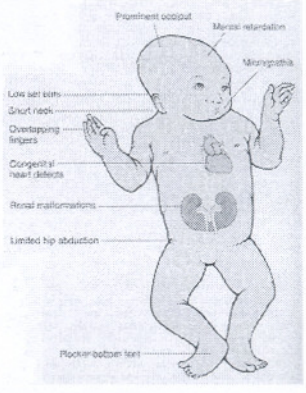


Consultant:Dr,Ghassan.Zidan

Trisomy 18 (Edward's syndrome)

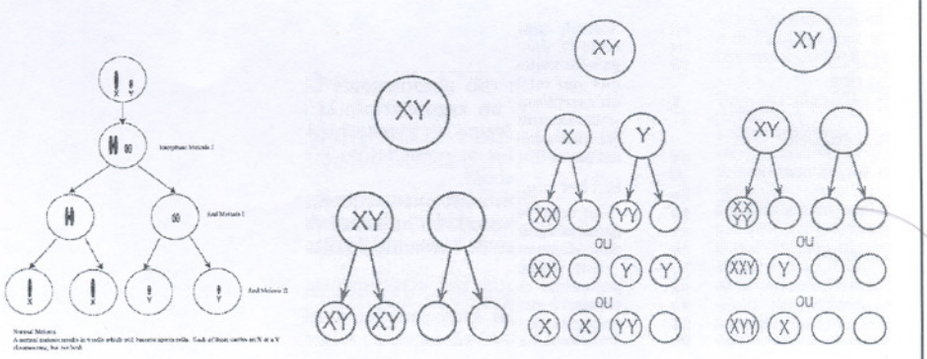
Incidence ~1 in 3000. Again most babies die in the first year and many within the first month.





Consultant:Dr,Ghassan.Zidan

Gonosomes



gametes O Y X XY YY XX XYY XXY XXYY

Homogeneous due to meiotic non-disjunction

Gonosomes

Various anomalies can occur

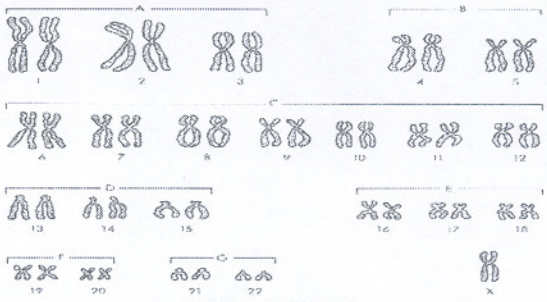
45,X.
47,XXX 47,XXY 47,XYY
48,XXXX 48,XXXY 48,XXYY
49,XXXXX 49,XXXXY

Consultant:Dr,Ghassan.Zidan

Gonosomes

Turner syndrome, 45, X

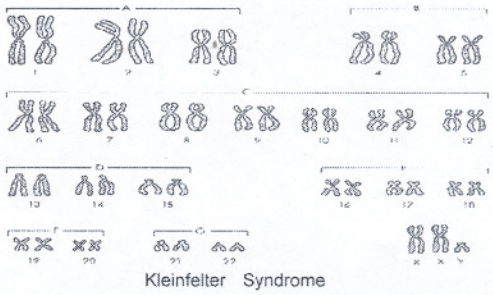
The incidence is about 1 in 500 female births, 99% of Turner syndrome embryos are spontaneously aborted.
Individuals are very short, they are usually infertile.
Characteristic body shape changes include a broad chest with widely spaced nipples and may include a webbed neck.
IQ and lifespan are unaffected.



Turner Syndrome

***Kleinfelter's syndrome*, 47, XXY**

The incidence at birth is about 1 in 1000 males.
Testes are small and fail to produce normal levels of testosterone which leads to breast growth (gynaecomastia) in about 40% of cases and to poorly developed secondary sexual characteristics.
There is no spermatogenesis.
These males are taller and thinner than average and may have a slight reduction in IQ.
Very rarely more extreme forms of Kleinfelter's syndrome occur where the patient has 48, XXXY or even 49, XXXXY karyotype. These individuals are generally severely retarded.



Kleinfelter Syndrome

47, XYY
Incidence 1 in 1000 male births. May be without any symptoms. Males are tall but normally proportioned. 10 - 15 points reduction in IQ compared to sibs, although they are fertile they do not seem to transmit the either this condition or Kleinfelter's syndrome.

XXX females
About one woman in 1000 has an extra X chromosome. 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 Kleinfelter's males

& (48,XXXX 48,XXXY 48,XXYY 49,XXXXX 49,XXXXY)

	mat	MI	MII	pat
Trisomie 21	93%	*75%*		
Trisomie 13	88%			
Trisomie 14	83%			
Trisomie 15	88%			
Trisomie 18	93%		*60%*	
Trisomie 16	~100%	*~100%*		
47,XXX	90%	*75%*		
47,XXY	53%			47%
47,XYY				100%
45,X				80%

chromosome abnormalities in early spontaneous abortions

Defect	frequency
triploidy	10%
tetraploidy	5%
trisomy	30%
Turner syndrome (45 X)	10%
other	5%
Total	60%

polyploidy.

Triploidies are the most frequent,

3N = 69 chromosomes: e.g. 69, XXX, or 69, XXY, or 69, XYY.
spontaneous miscarriages.

digyny
diandry

Tetraploidy,

4N = 92 chromosomes.
spontaneous miscarriages.

B - MOSAICISM

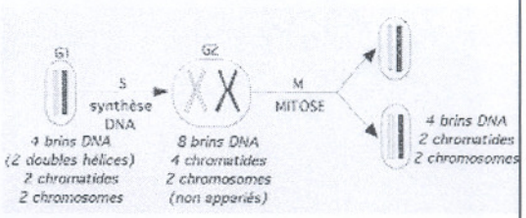
■A mosaic individual is made of 2 (or more) cell populations, come from only 1 zygote

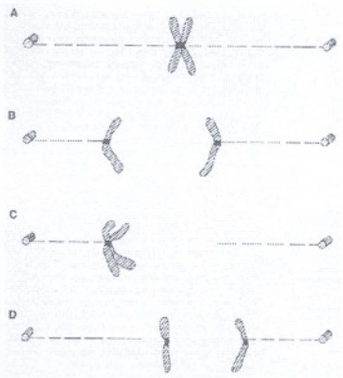
■ Is denoted by a slash between the various clones observed e.g.46, XY / 47, XY, +21).

■ Numerical mosaic anomaly is usually due to a mitotic non-disjunction:

■ Viability
■ phenotype
■ Variability of clone proportions

■A mosaic must not be confused with a chimaera.





II - STRUCTURAL ANOMALIES

A - Introduction

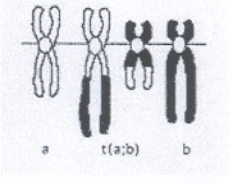
Visually, chromosomes can appear to break, and broken ends can rejoin in various ways:

- either as they were: restitution
- or, in case of 2 (or more) breaks, with interactive re-joining to make a structural aberration (exchanges).

- Of those that survive and are transmitted, the most frequent are
  - translocations,
  - small inversions
  - and deletions.

1 - Reciprocal translocation:

A mutual exchange between terminal segments from the arms of 2 chromosomes.

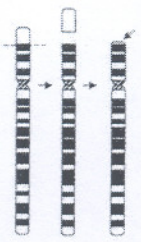


Provided that there is no loss or alteration at the points of exchange,

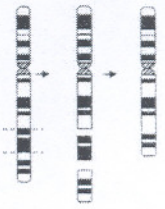
- Recorded as t or rcp (e.g. t(9;22)(q34;q11)).
- The carrier has a normal phenotype.

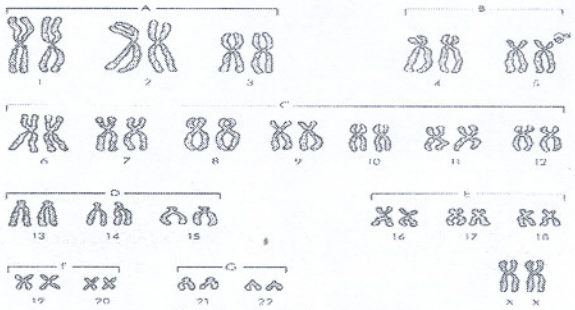
-They can occur de novo, or be transmitted through several generations.

Deletion



- **Loss of a segment, either interstitial or terminal, from a chromosome .**
- **Invariably, but not always, results in the loss of important genetic material. ".**
- **Recorded as del,**

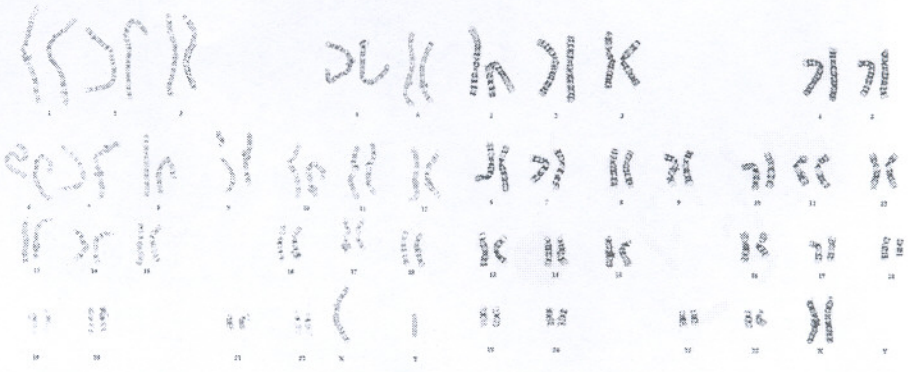




Cri-du-chat Syndrome

Deletion (del):

Terminal deletions: 46,XX,del(18)(q21.3).



Consultant:Dr,Ghassan.Zidan

Inversion

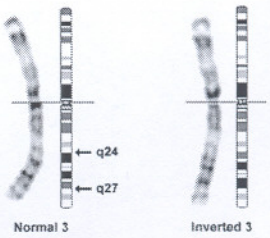
Inversion occurs when a segment of chromosome breaks, and rejoining within the chromosome effectively inverts it.

Recorded as inv.

Only large inversions are normally detected.

The carrier has a normal phenotype.

Paracentric inversion



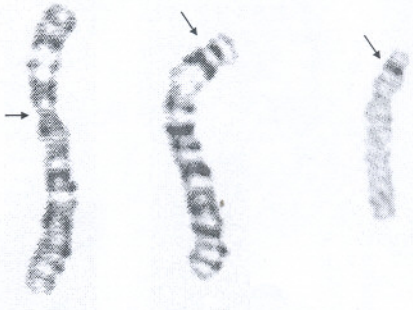
An inversion is termed paracentric when the segment involved lies wholly within one chromosome arm.

Are rare (or more likely rarely detected since the majority probably involve very small segments).

The most frequent paracentric inversions chromosomes 3, 7, and 14.

Pericentric inversion

An inversion is said pericentric when the two break-points involved are sited on opposite sides of the centromere,

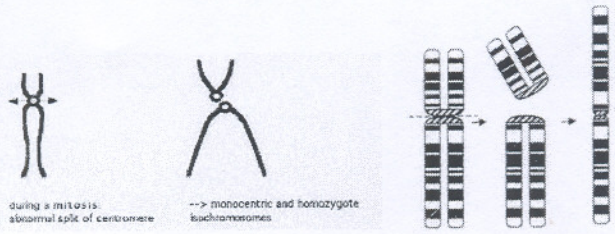


A pericentric inversion can provoke miscarriages, sterility (more often in the male), and lead to unbalanced products at meiosis.

Consultant:Dr,Ghassan.Zidan

Isochromosome :

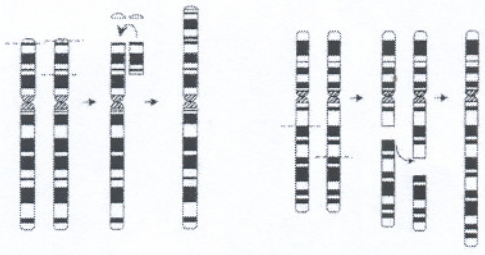
Loss of a complete arm, "replaced" by the duplication of the other arm



Consultant:Dr,Ghassan.Zidan

Duplication of a chromosome segment (dup):

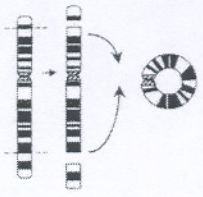
A segment of chromosome is repeated, once or several times, the duplicated segment keeping the same orientation with respect to the centromere



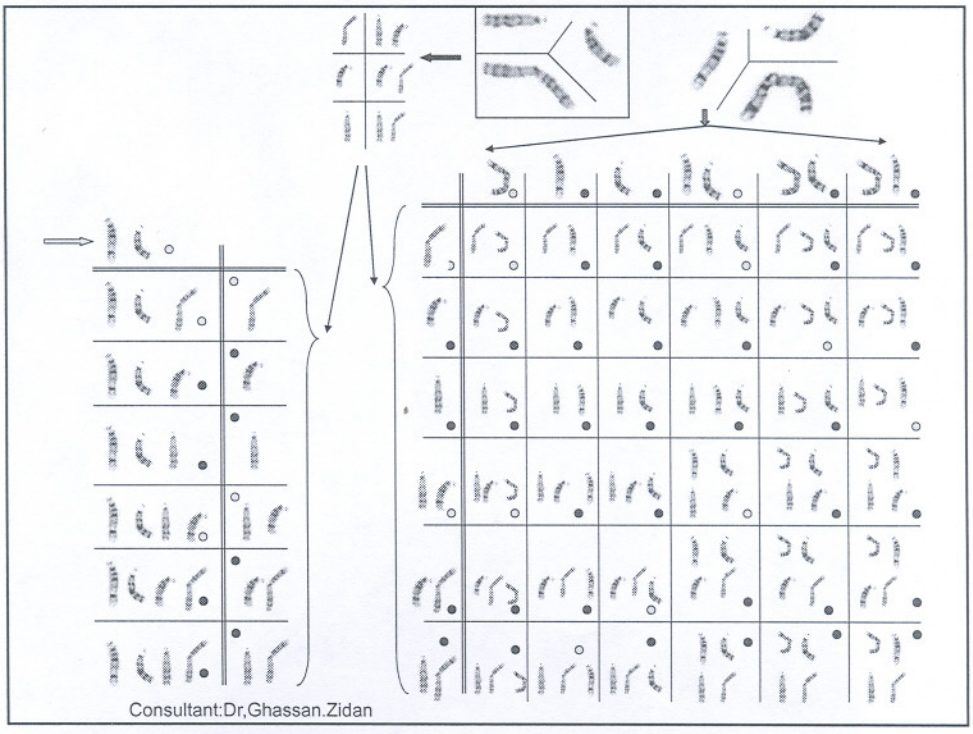
46,XX,dir dup(2)(q35q37.3).

Ring formation (Ring chromosome):

A centric ring involves the deletion (often small) of the ends of both arms (including the telomeres) and rejoining of the median segment to itself in a circular structure.



Consultant:Dr,Ghassan.Zidan



Consultant:Dr,Ghassan.Zidan