Basic Human Genetics: Reproductive Health and Chromosome Abnormalities

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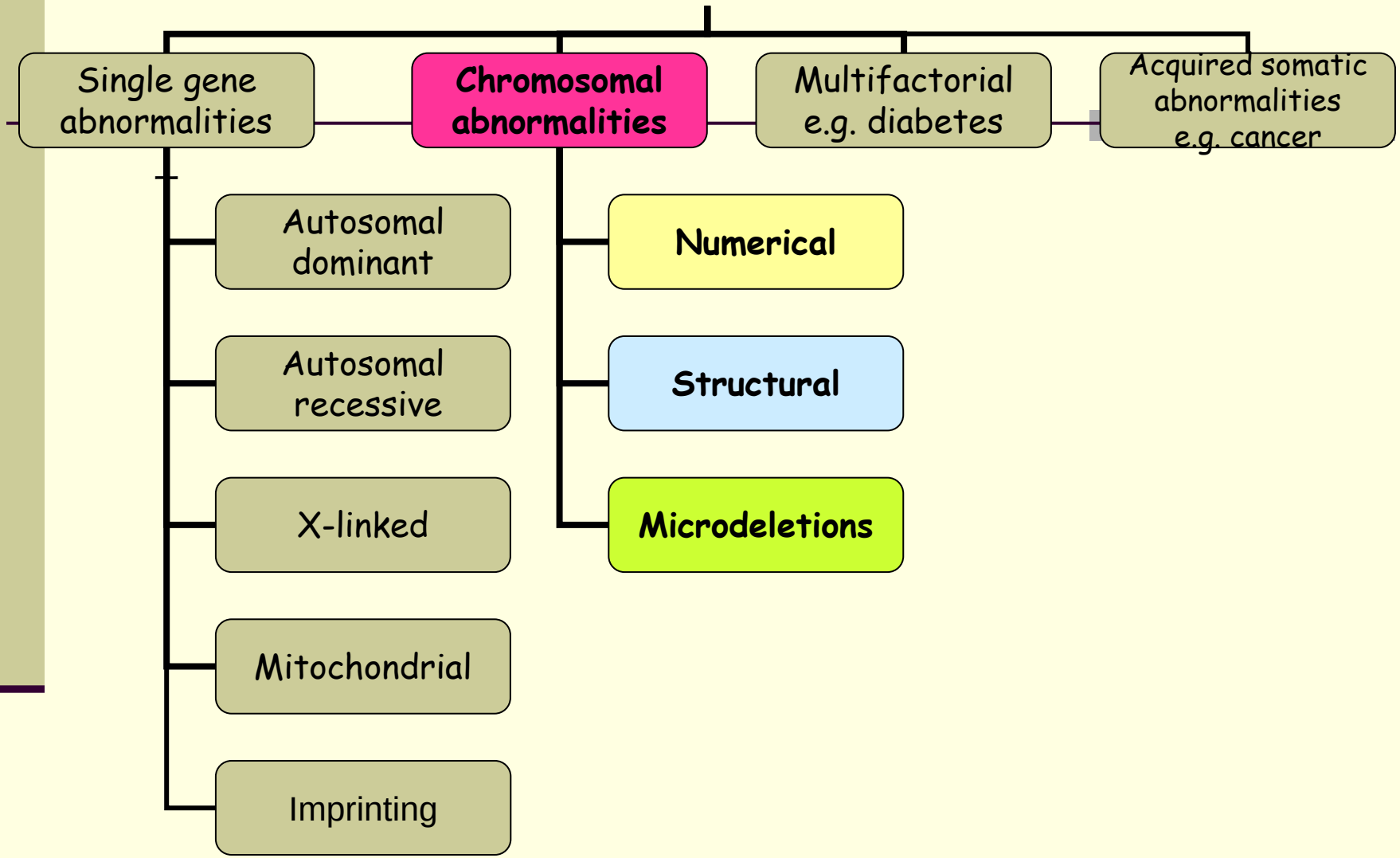
Categories of Genetic Diseases



Types of Chromosome Abnormalities

Numerical:

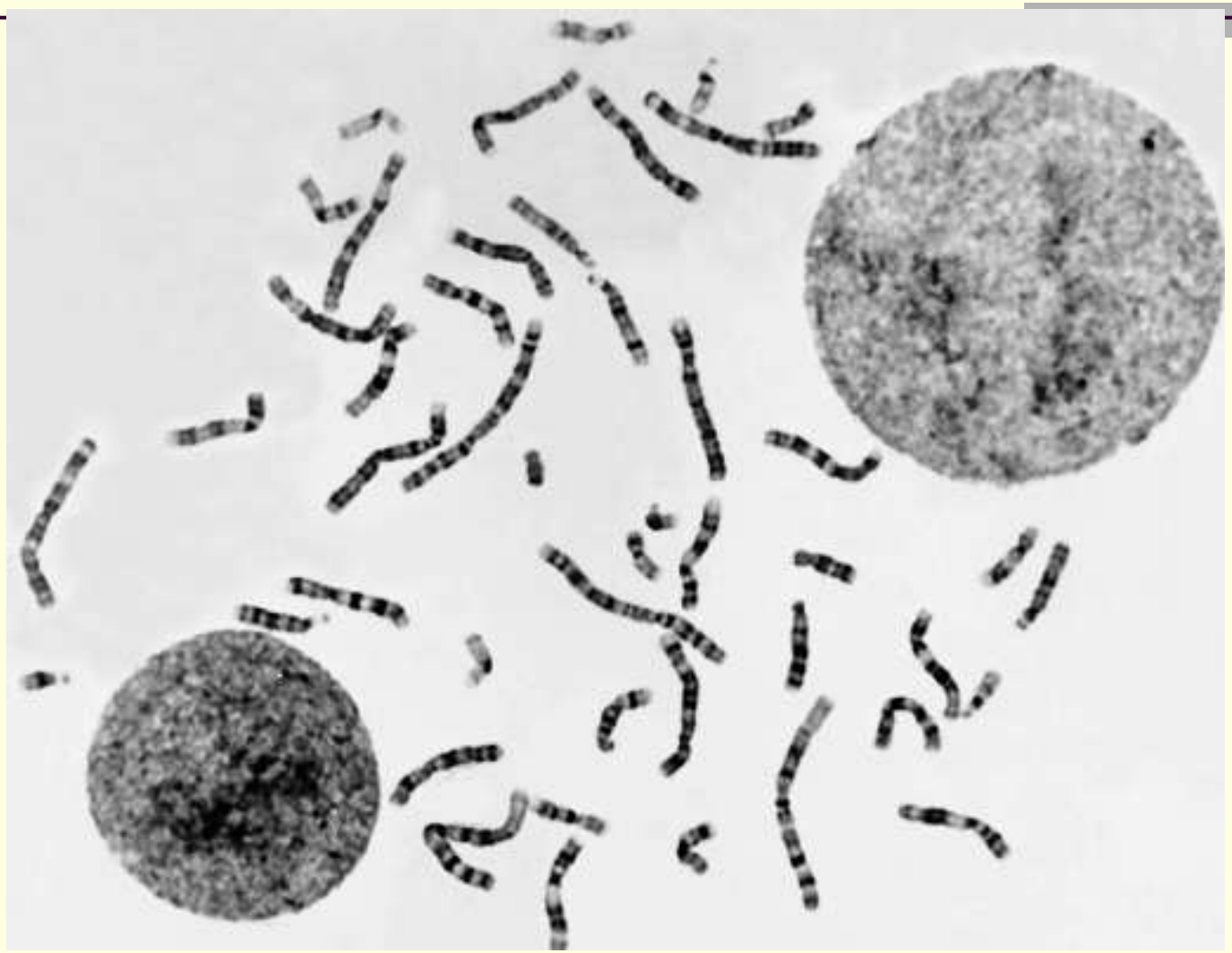
- Trisomy
- Monosomy
- Mosaicism
- Triploidy

Structural:

- Translocation
- Deletion
- Inversion

Microdeletions and microinsertions

46 Chromosomes in a human cell as seen under the microscope



Frequencies of chromosome abnormalities

A chromosome abnormality is present in 40-50% of all recognized first-trimester pregnancy loss. Approximately 1 in 6 of all pregnancies results in spontaneous miscarriage, thus around 5-7% of all recognized conceptions are chromosomally abnormal.

Birth prevalence of chromosome abnormalities is 0.5-1%

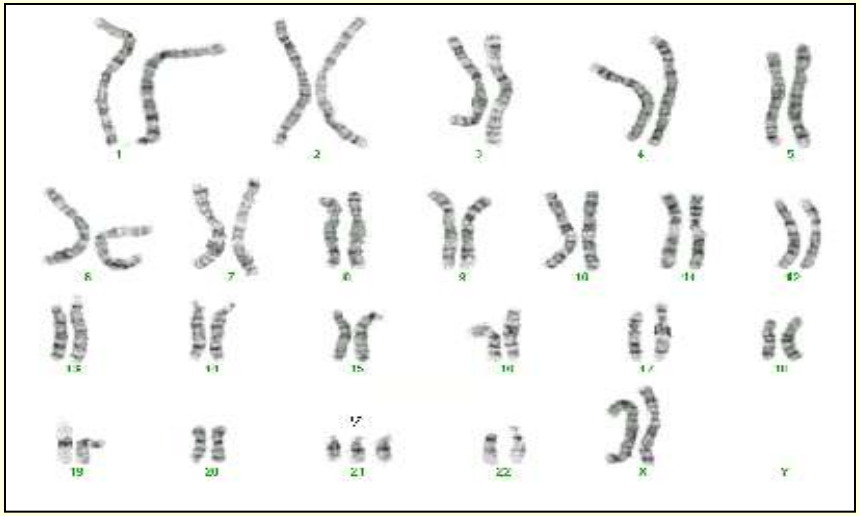
Chromosome abnormalities can cause:

- Infertility
- Repeated spontaneous abortions
- Stillbirths
- Infant mortality
- Birth defects
- Sexual ambiguity or abnormality in sexual development
- Unexplained short stature in female children

Trisomy

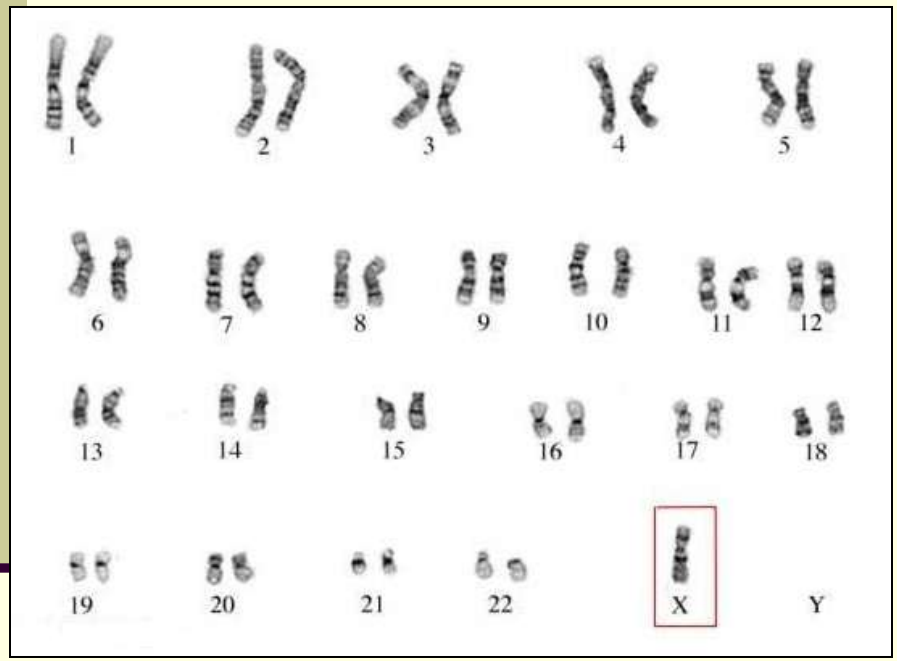
Presence of an extra chromosome, the total number of chromosomes is 47 in a somatic cell.

Trisomy usually results from meiotic non-disjunction



There are 3 of number 21 chromosomes in the above karyotype

Monosomy



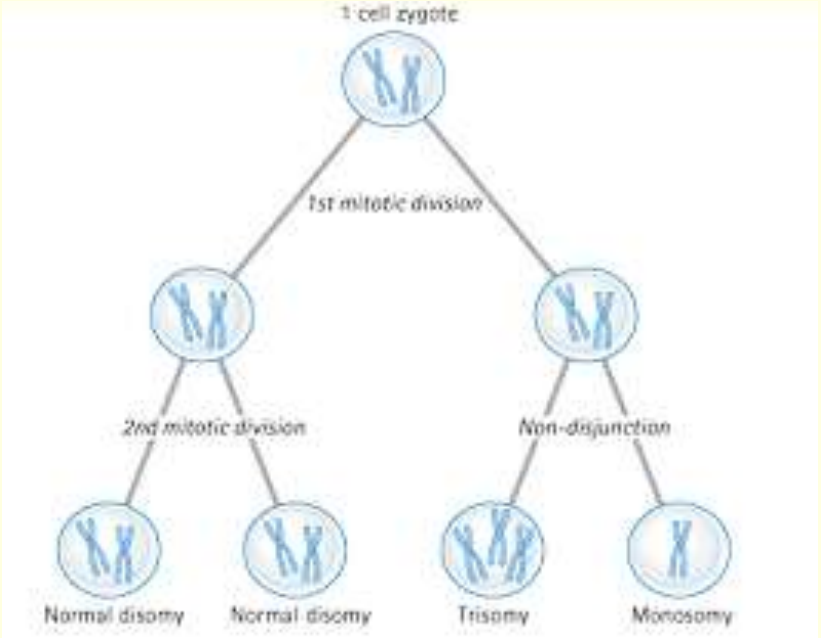
- absence of one chromosome, so the total number of chromosomes is 45 chromosomes in a somatic cell.
- usually only seen as 45,X, (autosomal monosomy is usually lethal)
- Monosomy usually results from meiotic non-disjunction

Mosaicism

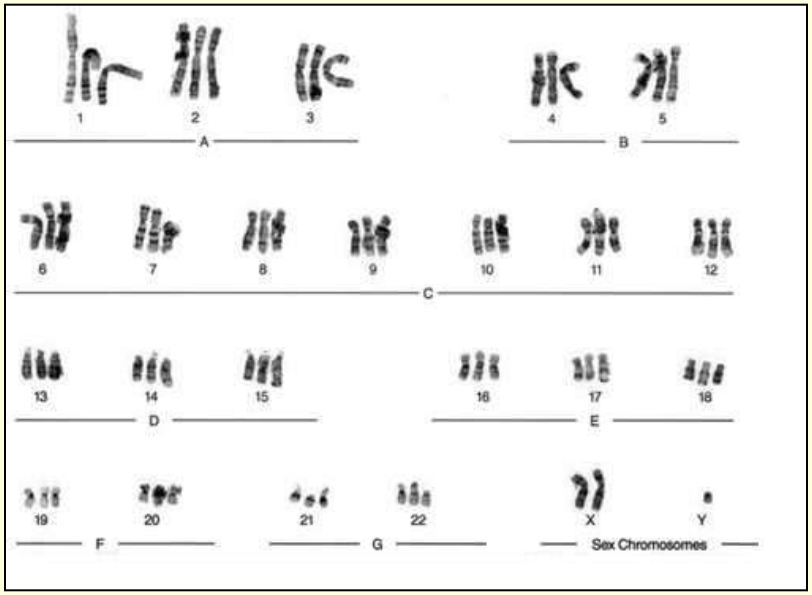
There are 2 types of cells in an individual,

for example normal 46,XY cells and abnormal trisomic cell line 47,XY,+21

The two cell lines are derived from the same zygote due to mitotic non-disjunction



Triploidy



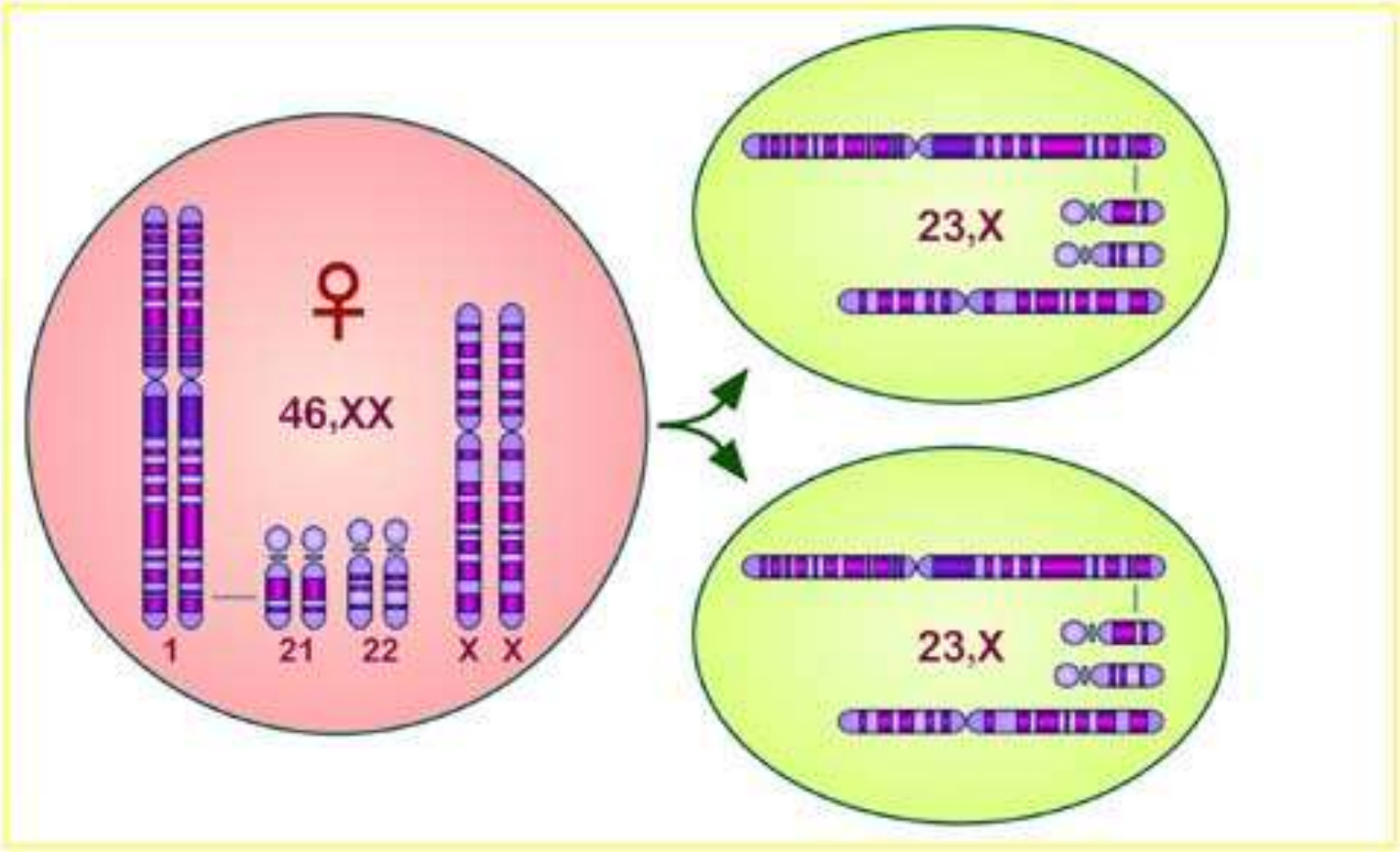
Presence of 3 haploid sets : 23 x 3 = 69 chromosomes

(haploid set = 23, diploid set = 46)

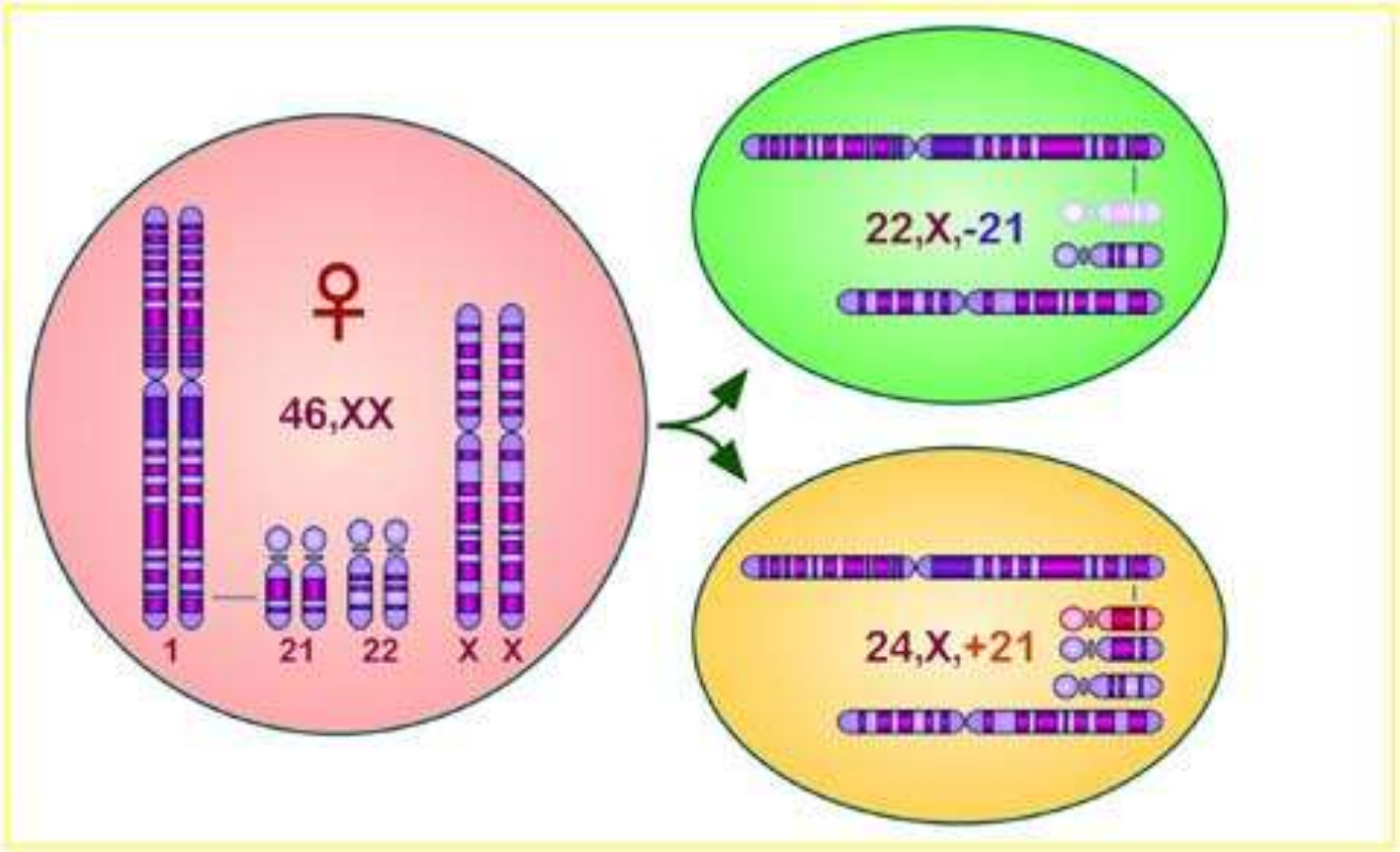
Usually incompatible with life and seen only in abortions.

May results from 2 sperms fertilising the ovum or retainment of the polar body with the ovum

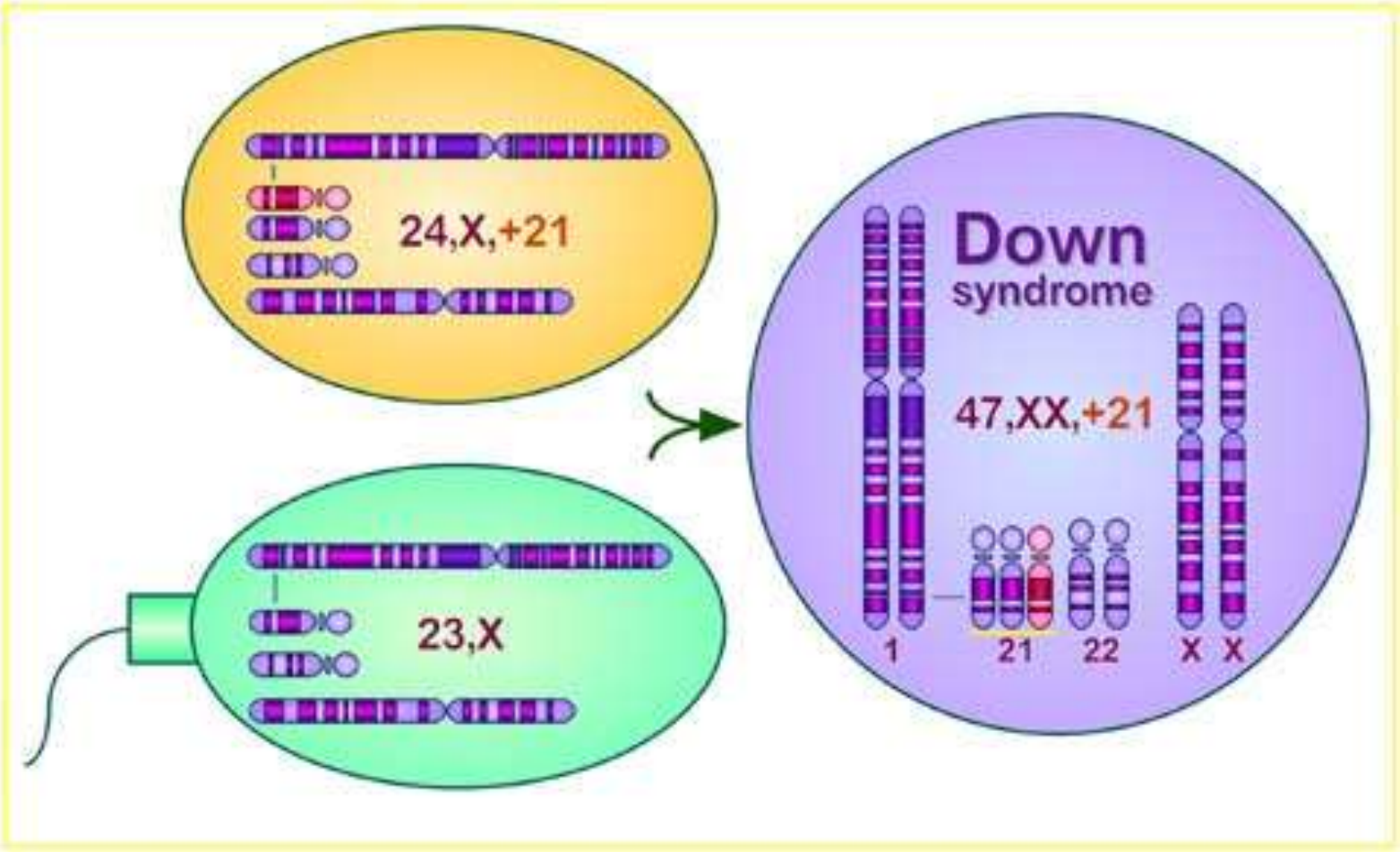
Normal meiosis, the 46 chromosomes become 23 in each gamete



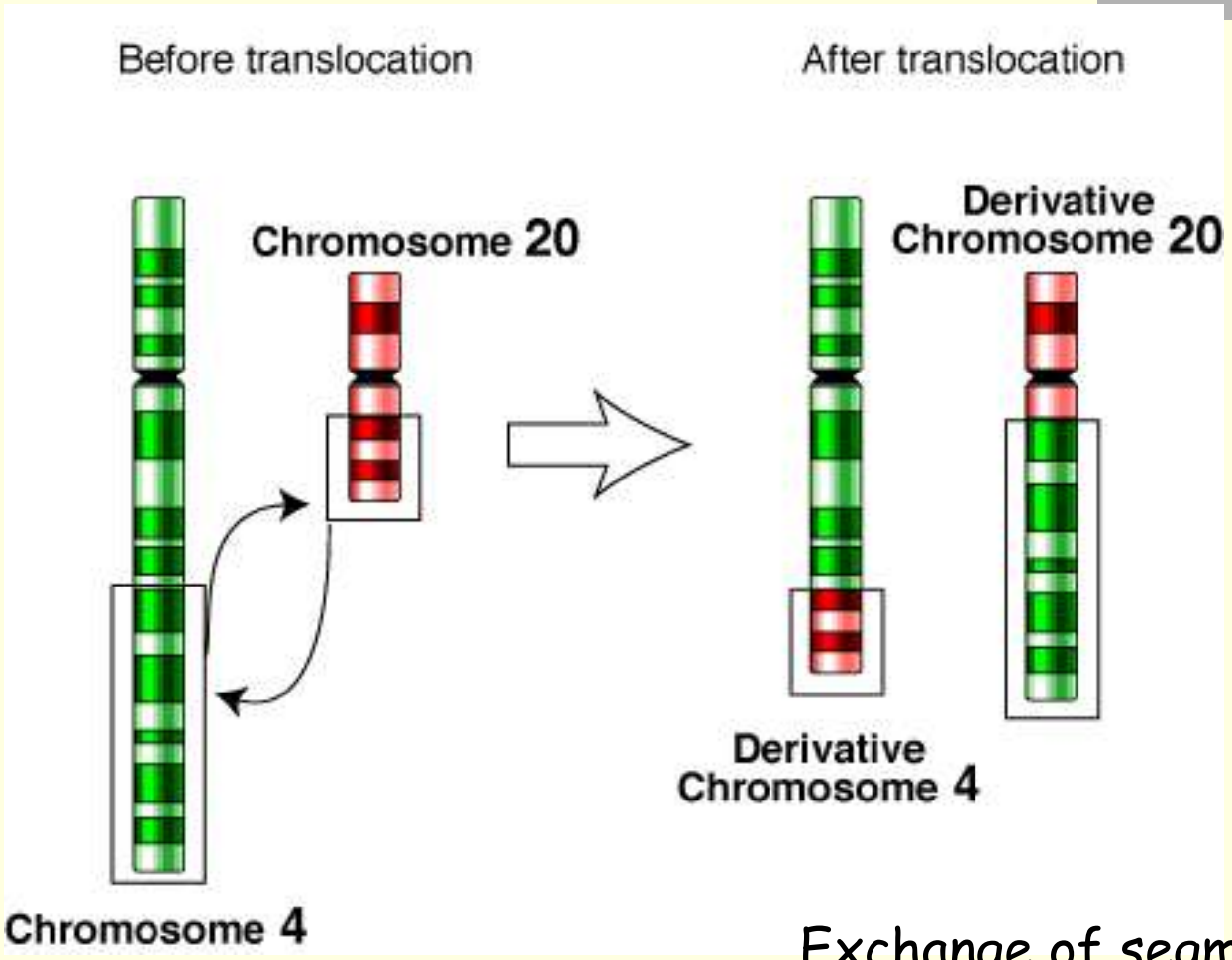
Non-disjunction during meiosis means that one daughter cell gets 24 chromosomes and the other 22 chromosomes



Fertilisation of the gamete carrying 24 chromosomes (extra number 21) with a normal gamete having 23 chromosomes results in a zygote of 47 chromosomes (trisomy 21 zygote)

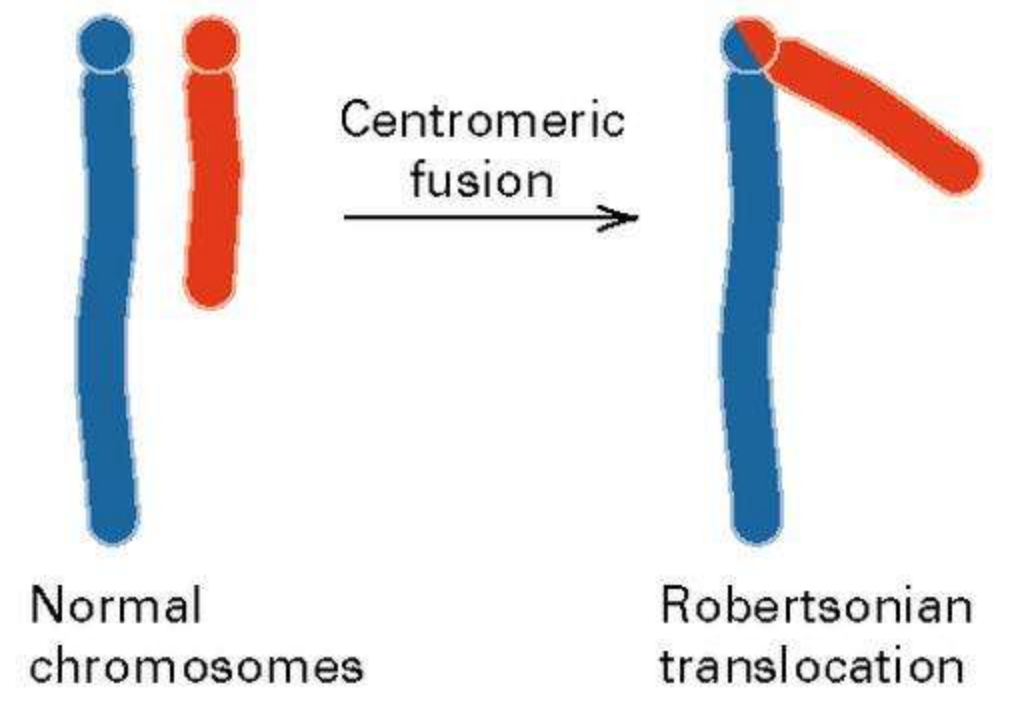


Reciprocal translocation = exchange of segments between 2 non-homologous chromosomes



Exchange of segments

Robertsonian translocation occurs between 2 acrocentric chromosomes with breaks near centromeres and union of the long arms



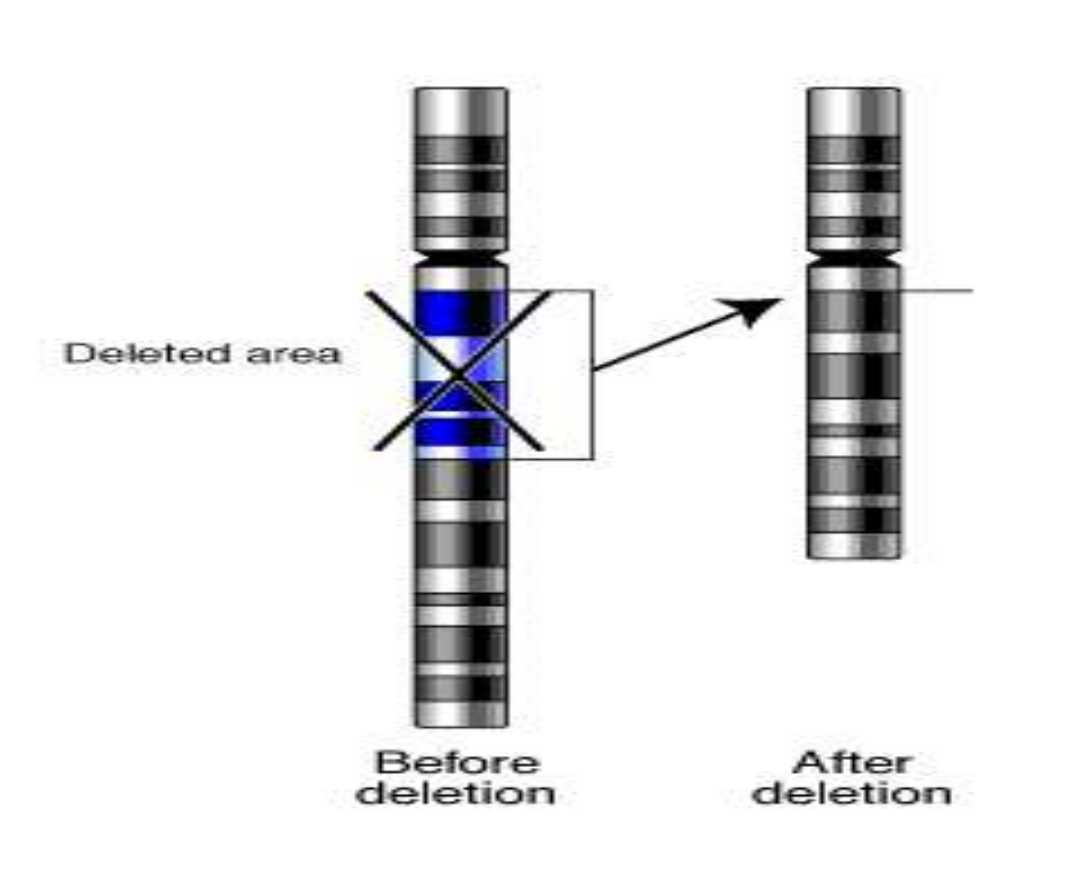
Carriers of balanced translocations are healthy but…

They are at risk of having offspring with unbalanced unbalanced chromosome constitution

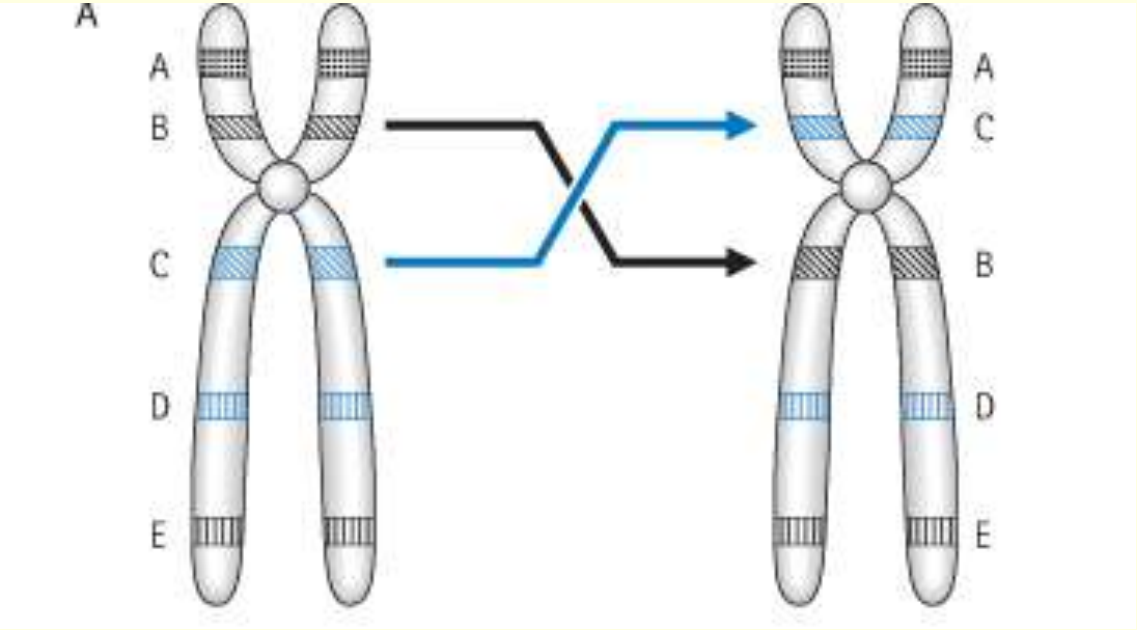
This may present as:

- Rrepeated spontaneous abortions
- Stillbirths
- Birth defects

Deletion: loss of part of a chromosome



Pericentric inversion: two breaks with inversion of the segment in between



Karyotype description

- 46,XX normal female kayotype
- 46,XY normal male kayotype
- 45,X monosomy X= Turner syndrome
- 47,XY,+21 trisomy 21= Down syndrome
- 46,XY, 5p- deletion of part of short arm of chromosome 5 =Cri du Chat syndrome
- 46, XX, t(2;4)(q22;q23) translocation between long arms of chromosomes 2 and 4 with breakpoints at region 2 band 2 for chromosome 2 and region 2 band 3 for chromosome 4.

Consequences of chromosome abnormalities

- Infertility : examples: Turner and Klinefelter syndromes
- Repeated spontaneous abortions: healthy carriers of translocations and inversions
- Stillbirths and infant deaths: where the chromosme abnormality is very severe for example trisomy 13 and trisomy 18
- Congenital disorders : for example Down syndrome , microdeletion syndromes

Syndromes with chromosome abnormalities

Chromosome abnormalities at birth

Trisomy 13	0.2/1000 births
Trisomy 18	0.3/1000 births
Trisomy 21	1.5/1000 births
45,X	0.2/ 1000 female births
47XXX	1/1000 female births
47,XXY	1/1000 male births
47,XYY	1/1000 male births
Other unbalanced rearrangements	**1/1000 births**
Balanced rearrangements Total	**3/1000 births**

Down syndrome (DS)

The overall prevalence at birth is approximately 1 in 650 to 1 in 700 births

May be higher in some countries where women continue to bear children at an advanced age, for example : among 63,398 newborns in Dubai, UAE, (1999-2003), prevalence was

3.13/1000 births for nationals and

1.66/1000 births for non UAE

(Murphy 2007)

Clinical features of DS

The most common finding in the newborn period is severe hypotonia.

Single palmar creases are found in 50% of Down syndrome children in contrast to 2-3% of the general population.

Congenital cardiac abnormalities are present in 40-45% of babies with Down syndrome.

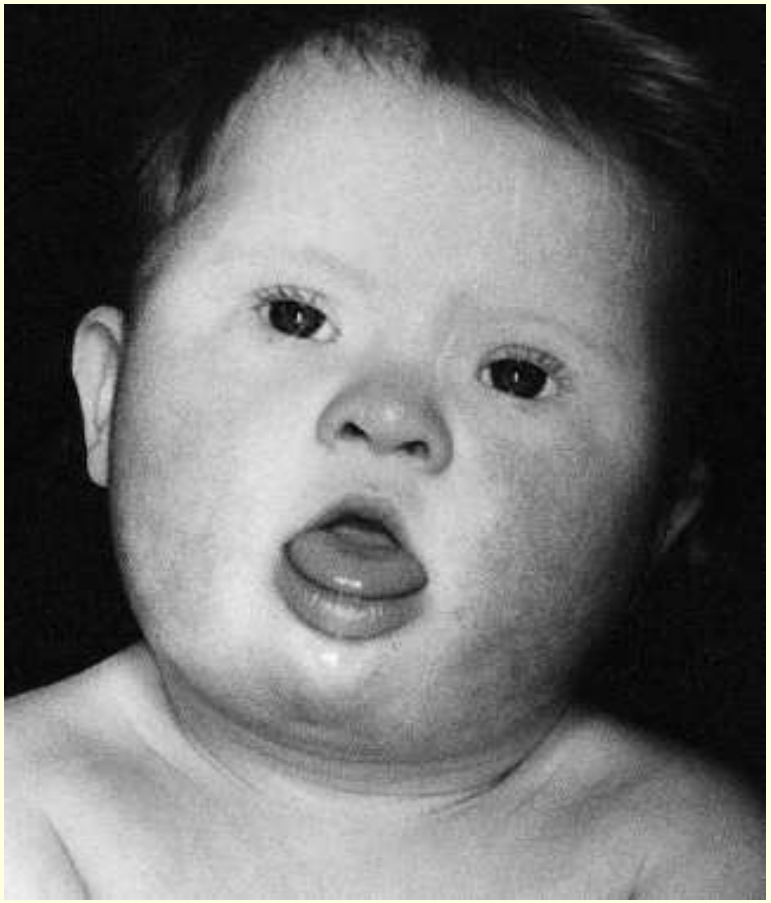
Hypothyroidism.

Facial features of DS

upward sloping palpebral fissures

small ears

protruding tongue



Upward sloping palpebral fissures,

Brushfield spots and bilateral epicanthic folds.

Natural history of DS

Affected children show a broad range of intellectual ability with IQ scores ranging from 25 to 75. The average IQ of young adults with Down syndrome is around 40 to 45.

Social skills are relatively well advanced and most children with Down syndrome are happy and very affectionate.

Natural history of DS

Adult height is usually around 150 cm.

In the absence of a severe cardiac anomaly, which leads to early death in 15-20% of cases, average life expectancy is 50-60 years.

Most affected adults develop Alzheimer disease in later life due to dosage effect of the amyloid precursor protein gene

Chromosome abnormalities in Down syndrome

95% of cases are trisomy 21 , 47,XX,+21 (47,XY,+21), risk of having trisomy 21 increases with advanced maternal age.

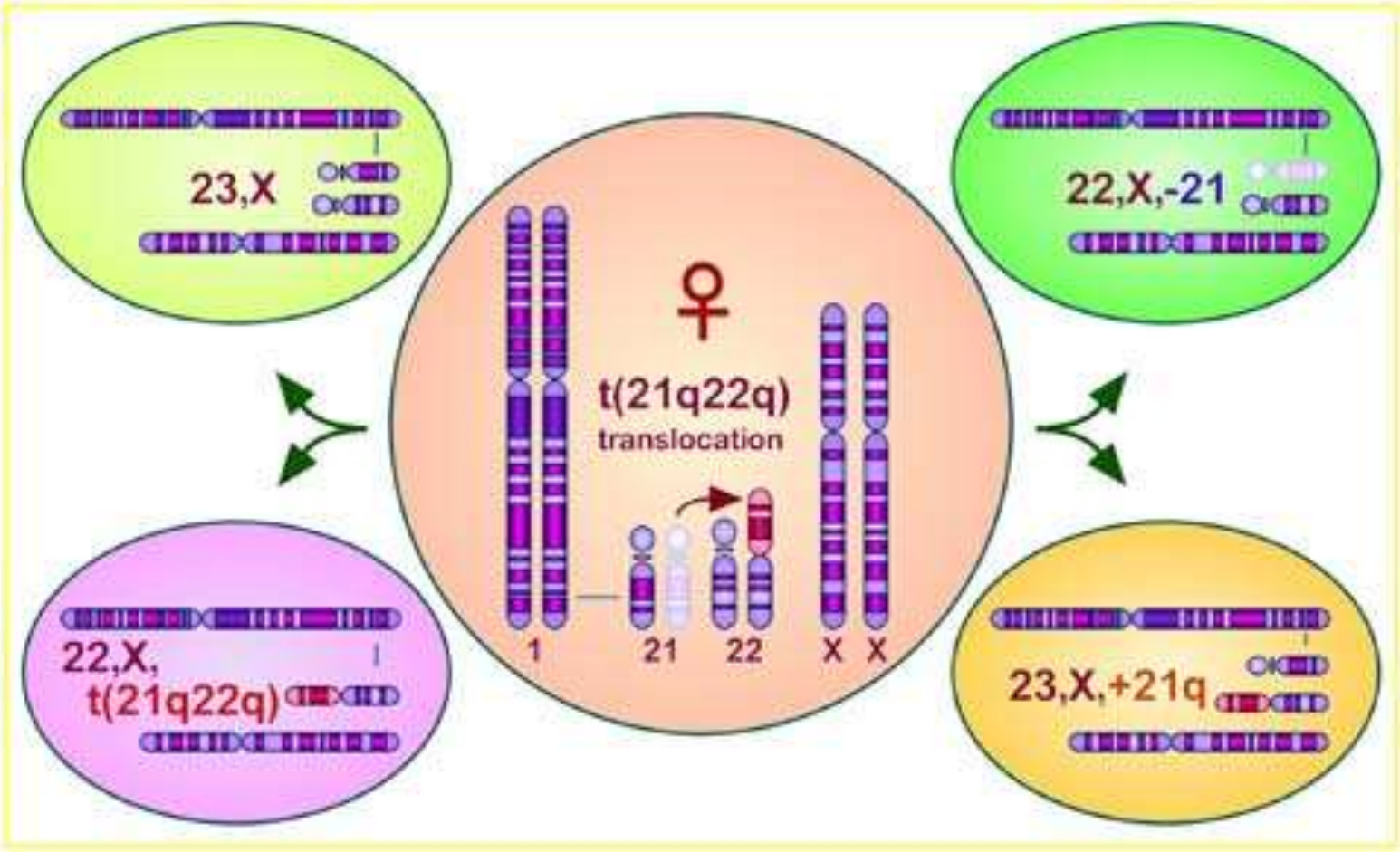
4% are due to translocation between chromosome 21 and another acrocentric with a total number of chromosomes =46 , but the genetic material of chromosome 21 is present in triplicate. The translocated chromosome is usually inherited from a normal carrier parent. Such a translocation carrier parent has a risk of having a Down syndrome with each pregnancy (about 20% if mother is carrier and 5% if father is carrier)

1% mosaic cases (46,XY/47,XY,+21)

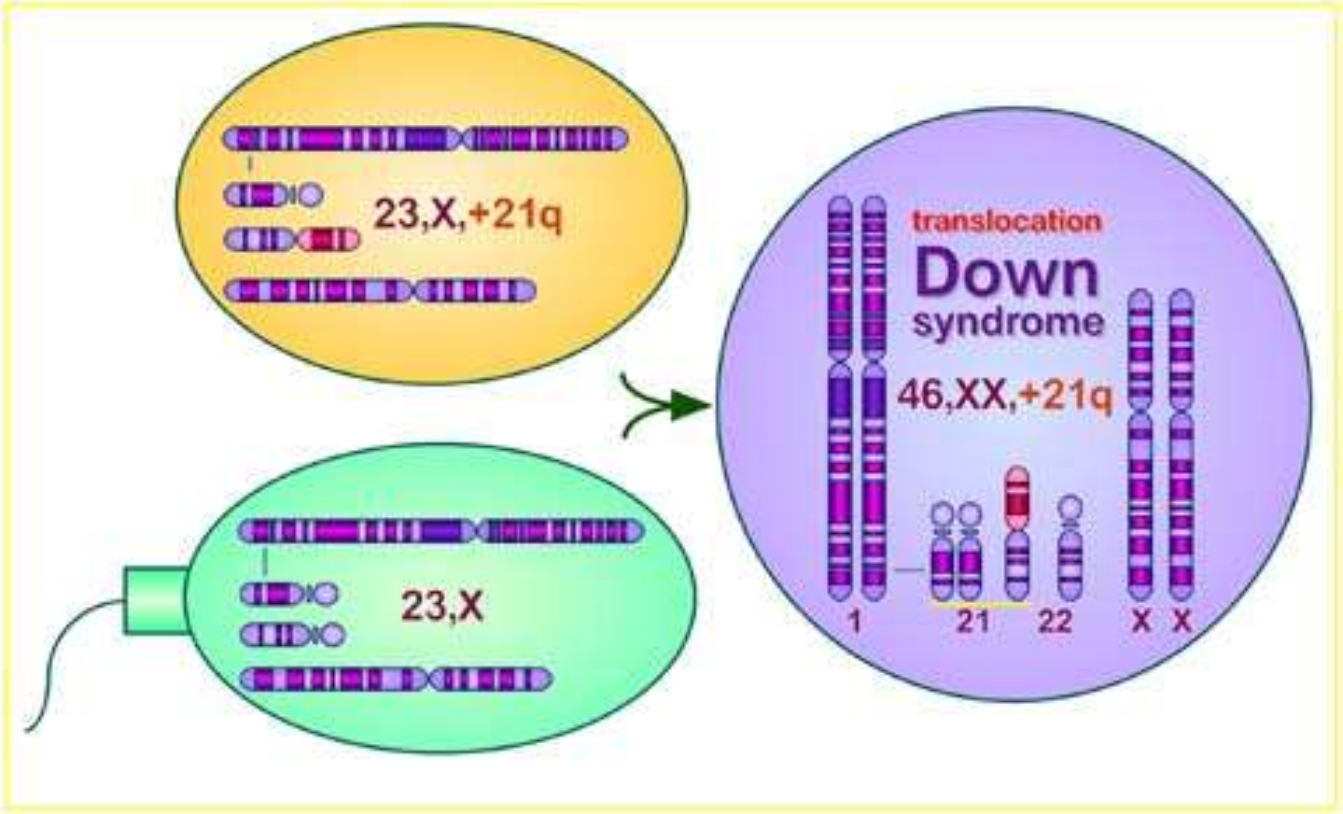
Risk of Down's Syndrome and Chromosomal Abnormalities at Live Birth, According to Maternal Age.		
Maternal Age at Delivery (yr)	Risk of Down's Syndrome	Risk of Any Chromosomal Abnormality
20	1/1667	1/526
25	1/1200	1/476
30	1/952	1/385
35	1/378	1/192
40	1/106	1/66
45	1/30	1/21

Salihu, 2003, Obstet Gynecol

Meiosis in Robertsonian translocation carrier who has 45 chromosomes (only one 21) but the other chromosome 21 is translocated to chromosome 22 = normal amount of genetic material



The gamete carrying 23 chromosomes but one is a translocation 21/22 is fertilised by a normal gamete resulting in a zygote with translocation Down syndrome

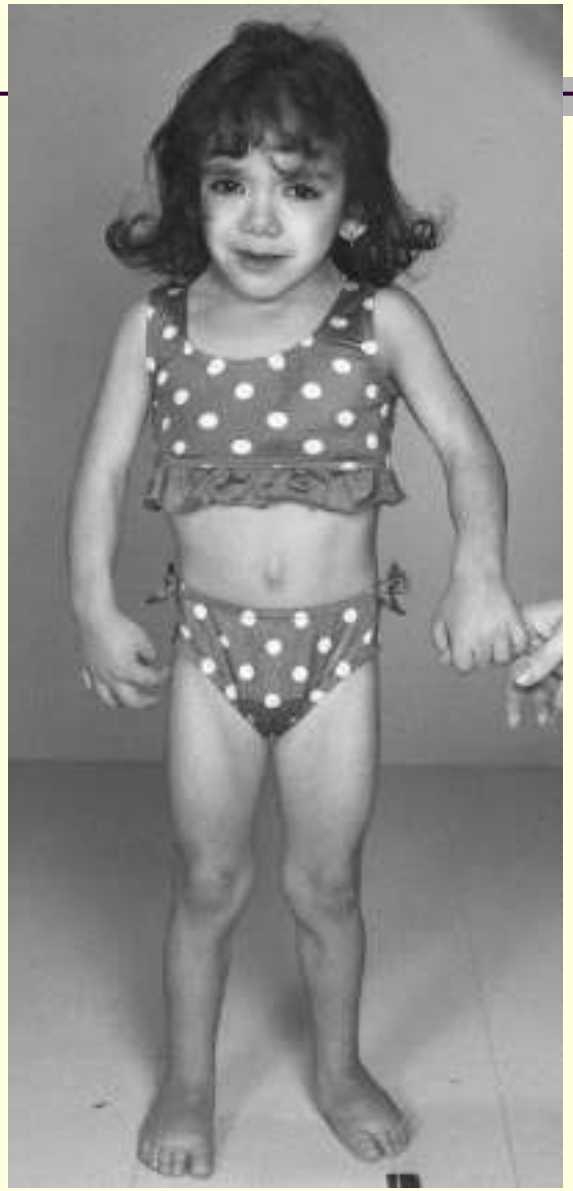


Turner syndrome: monosomy X

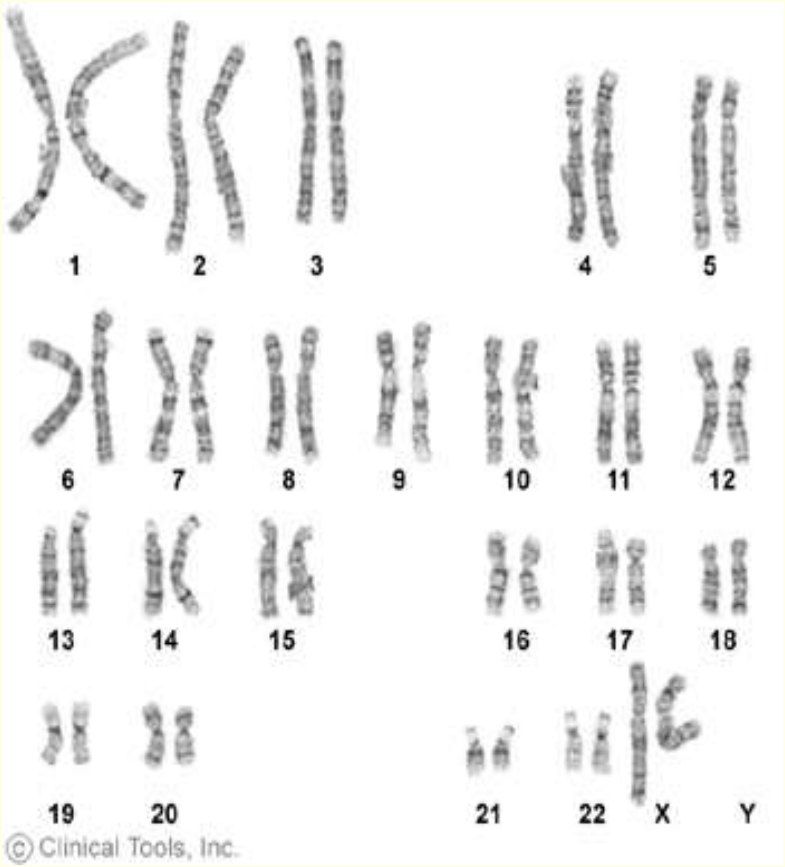
The two main medical problems are short stature and ovarian failure.

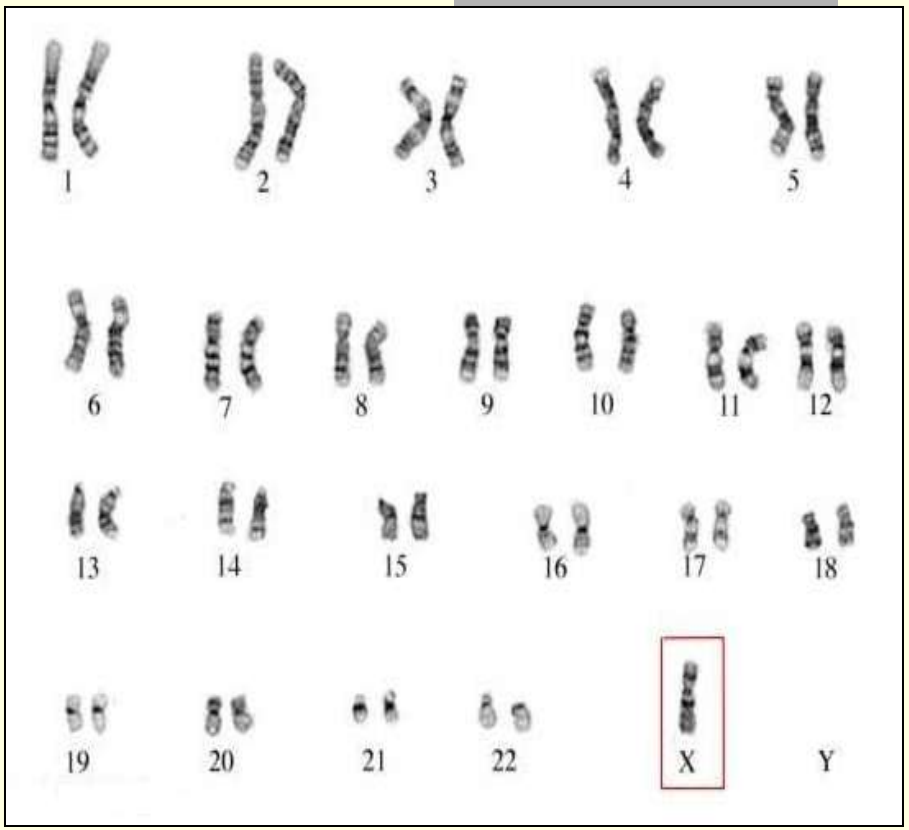
Ovarian failure leads to primary amenorrhea and infertility.

Estrogen replacement therapy should be initiated at adolescence for the development of secondary sexual characteristics and long-term prevention of osteoporosis

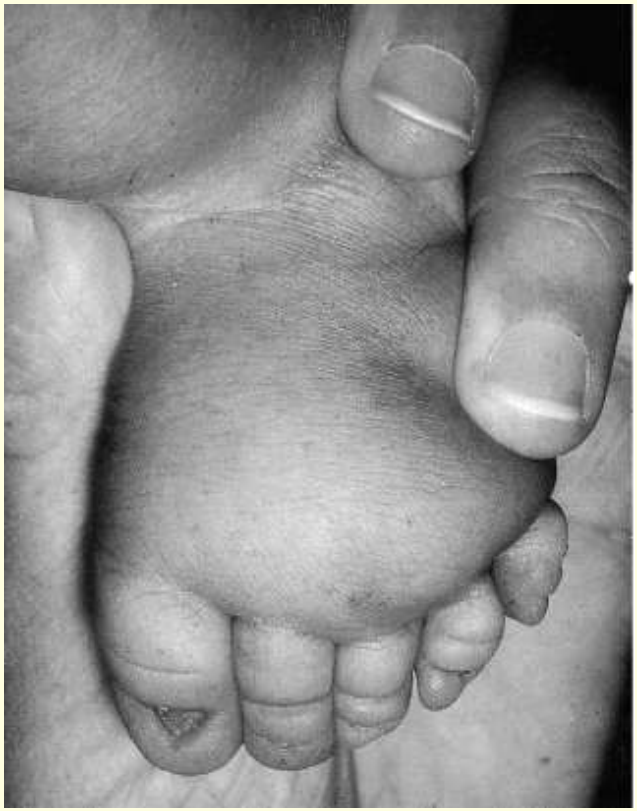


Normal female karyotype and Monosomy X





Turner syndrome features



- lymphedema at birth
- low posterior hair-line
- increased carrying angles at the elbows
- short fourth metacarpals
- widely spaced nipples
- coarctation of the aorta present in 15% of cases.

Chromosome anomalies in Turner syndrome

45,X = 50%

mosaics: 46,XX/45,X = 35%

Structural abnormalities

(deletion, isochromosome, ring X)

Turner syndrome is being detected early in pregnancy as a result of routine detailed ultrasound scanning, which can reveal either generalized edema (hydrops) or swelling localized to the neck (nuchal cyst or thickened nuchal pad) .

Klinefelter syndrome: 47,XXY

- Infertility
- Hypogonadism
- Diminished secondary sexual characters
- Clumsiness or mild learning difficulties. The overall verbal IQ is reduced by 10-20 points below that of unaffected siblings and controls
- 30% of adult males will show gynecomastia (enlargement of the breasts)

Chromosome abnormalities in Klinefelter syndrome

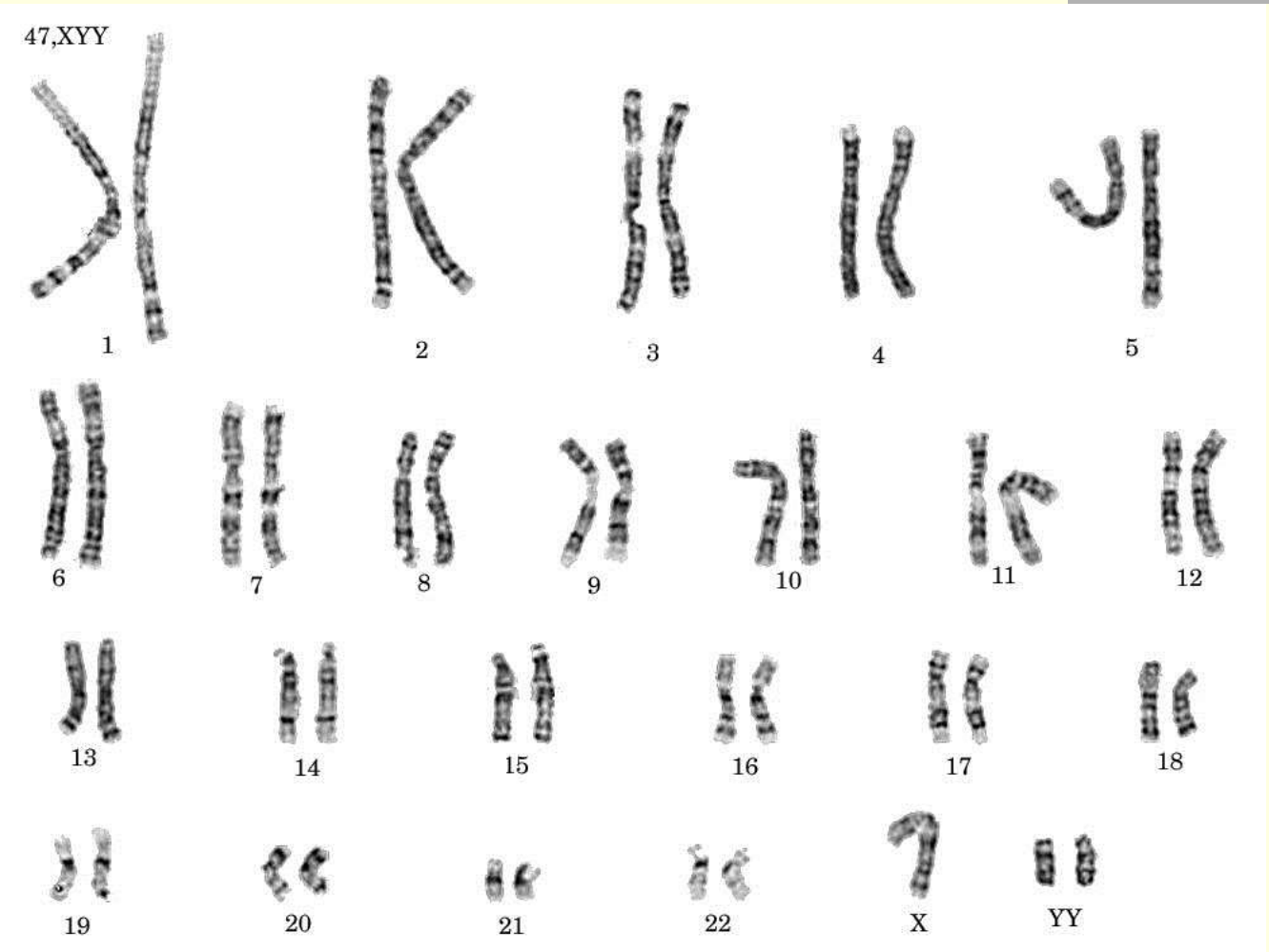
47,XXY

48,XXXY, 48,XXYY

49,XXXXY

46,XY/47,XXY

XYY male



XYY MALES

Fertility is normal.

Physical appearance is normal and stature is usually above average.

Intelligence is mildly impaired, with an overall IQ score of 10-20 points below a control sample.

The additional Y chromosome must arise as a result of non-disjunction in paternal meiosis II or as a post-zygotic event.

XXX females

These women usually have no physical abnormalities but can show a mild reduction of between 10 and 20 points in intellectual skills below their siblings. This is rarely of sufficient severity to require special education.

Women with a 47,XXX karyotype usually show normal fertility and have children with normal karyotypes.

Chromosome microdeletion syndromes

Prader-Willi syndrome

- **Hypotonia**
- **Poor sucking and feeding in neonates**
- **Fair skin and hair**
- **Downturned mouth corners**
- **Hyperthermia**
- **Gestational history of diminished fetal movements**
- **Hyperphagia and obesity**
- **Short stature**
- **Small hands and feet**
- **Mental subnormality**
- **Narrow bifrontal diameter**
- **Hypogonadotropic hypogonadism**
- Caused by microdeletion of paternal 15q11.2-12 (75%)

Diagnosis of microdeletion syndromes

FISH techniques using specific probes

Array comparative genomic hybridisation (array CGH)

Microdeletions cannot be detected in the banded karyotype

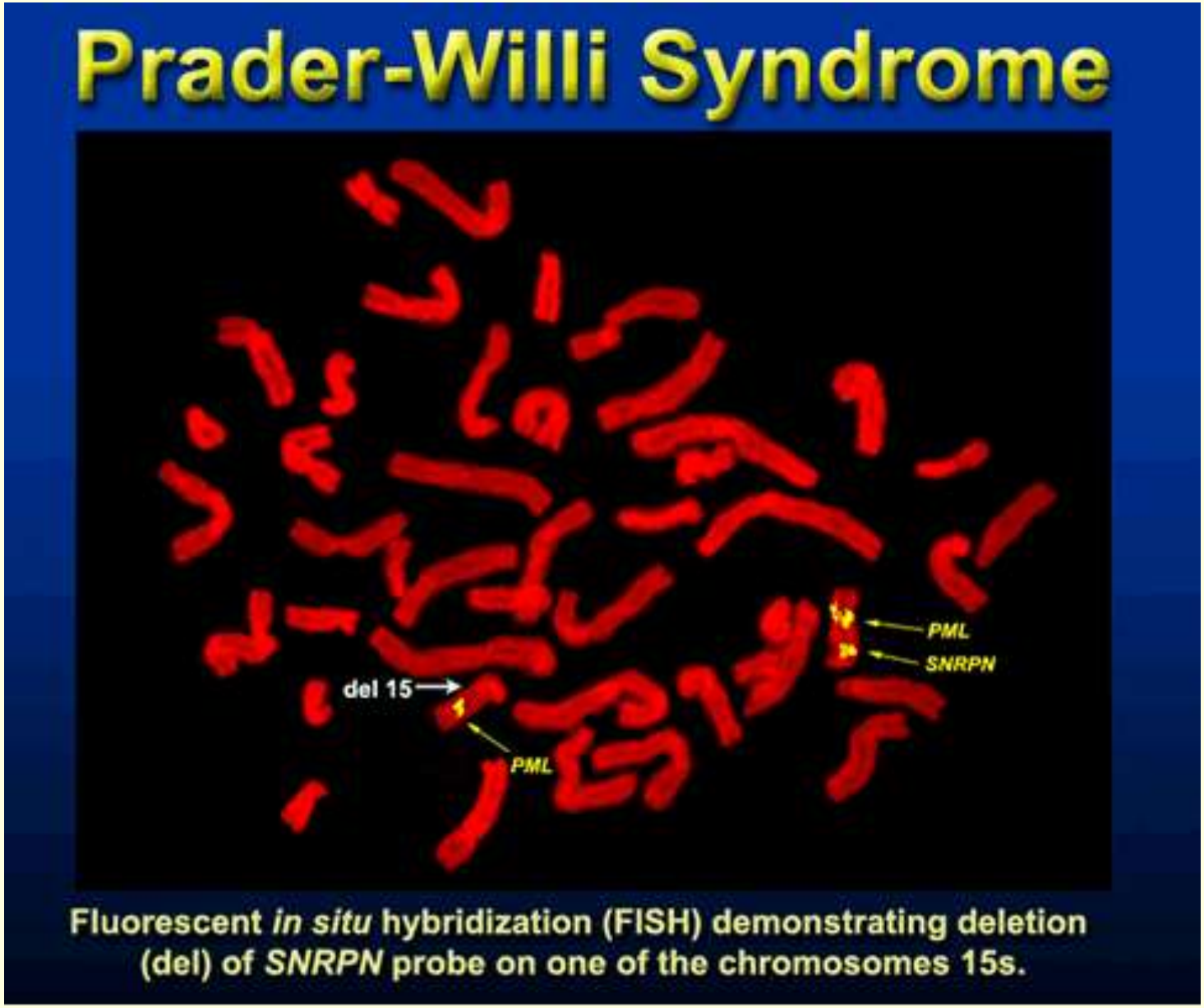

Prader-Willi Syndrome
PML
SNRPN
del 15
PML
Fluorescent *in situ* hybridization (FISH) demonstrating deletion (del) of *SNRPN* probe on one of the chromosomes 15s.

Figure 1

Indications for chromosome analysis in lymphocytes

- Multiple congenital abnormalities
- Unexplained mental retardation
- Sexual ambiguity or abnormality in sexual development
- Infertility
- Recurrent miscarriage
- Unexplained stillbirth
- Unexplained short stature in female children
- Malignancy and chromosome breakage syndromes

Conclusions

- Around 20,000 chromosome abnormalities have been registered on laboratory databases
- Chromosome abnormalities contribute to about 8% of all birth defects
- Chromosome abnormalities can be diagnosed in the fetus through chorion villus biopsy or amniocentesis (prenatal diagnosis), or by preimplantation genetic diagnosis following IVF