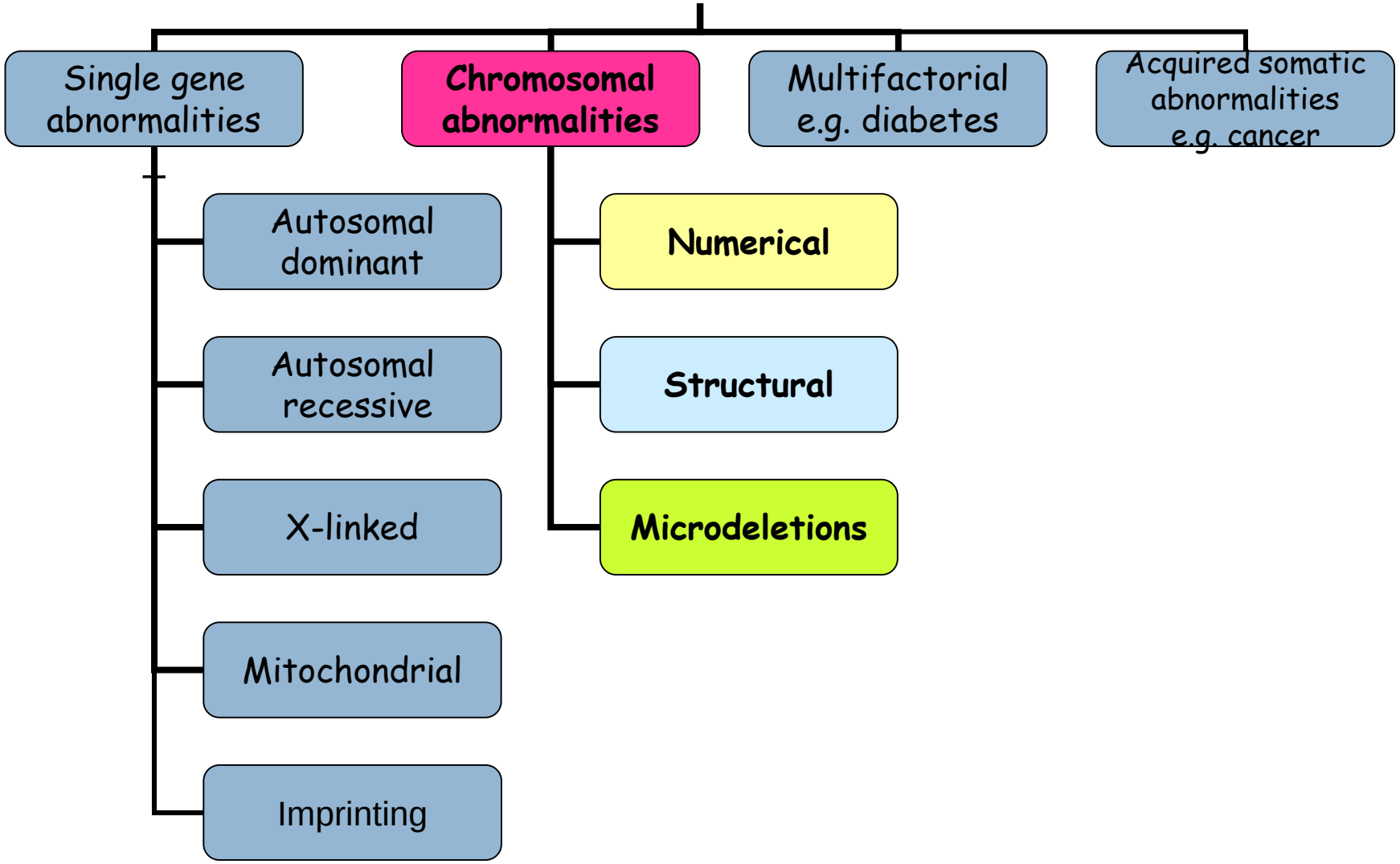
Basic Human Genetics: Reproductive Health and Chromosome Abnormalities

Professor Hanan Hamamy

Department of Genetic Medicine and Development
Geneva University
Switzerland

Training Course in Sexual and Reproductive Health Research - Geneva 2016

Categories of Genetic Diseases



Types of Chromosome Abnormalities

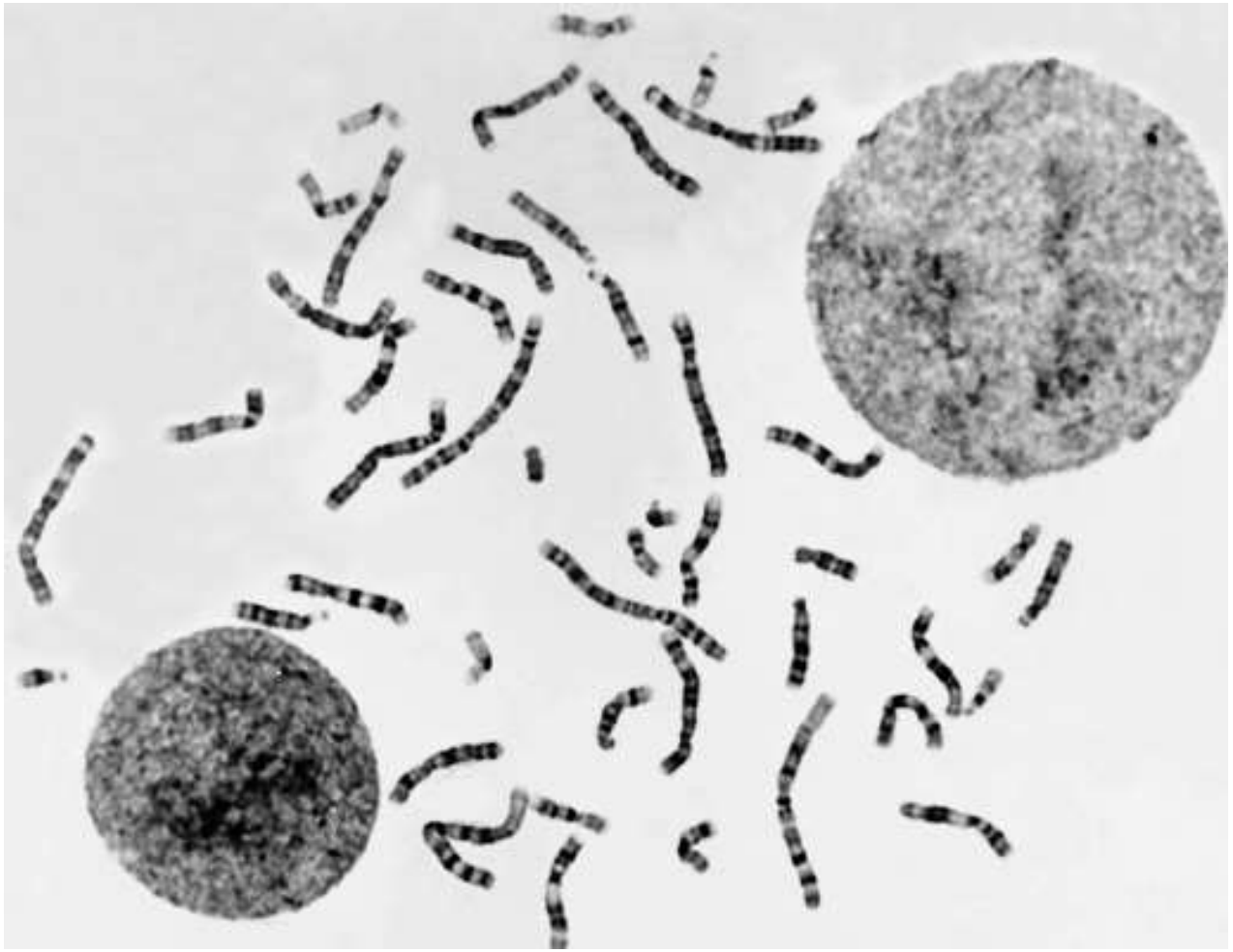
Numerical:

- Trisomy
- Monosomy
- Mosaicism
- Triploidy

Structural:

- Translocation
- Deletion
- Inversion
- Microdeletions & 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
- Birth prevalence of chromosome abnormalities is 0.5-1%

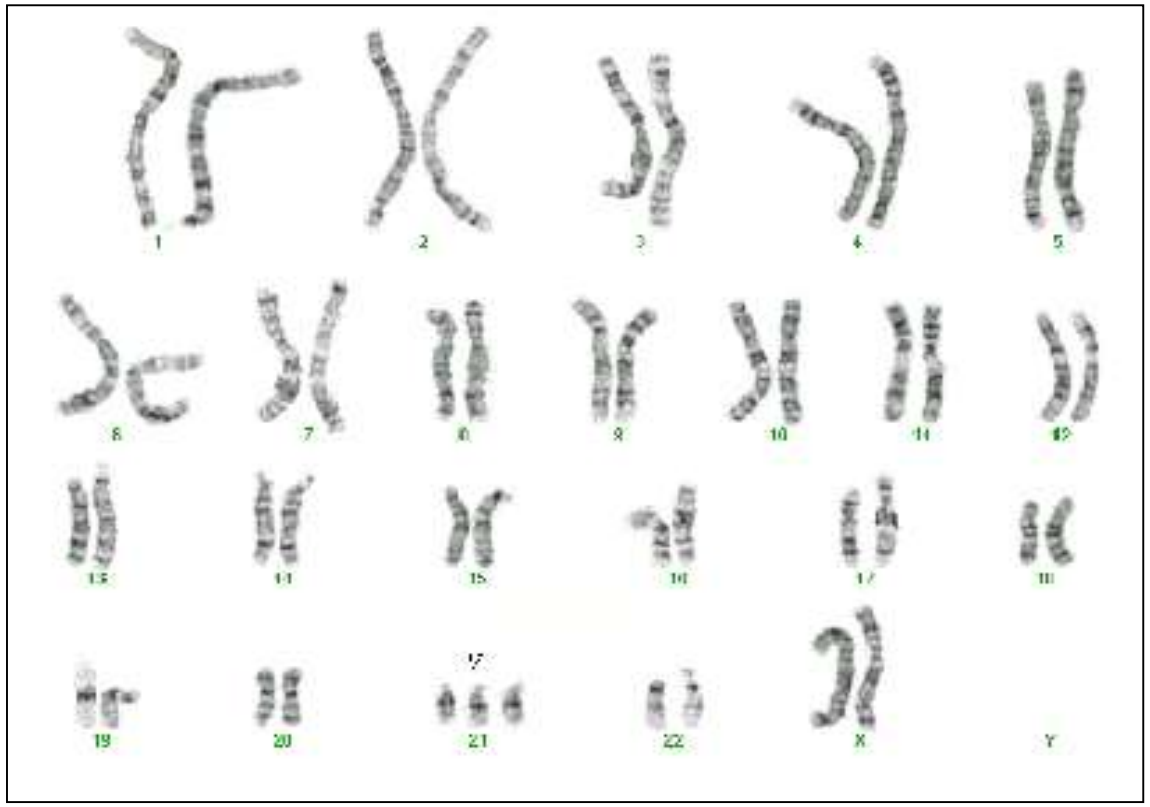
Chromosome abnormalities can cause:

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

Trisomy

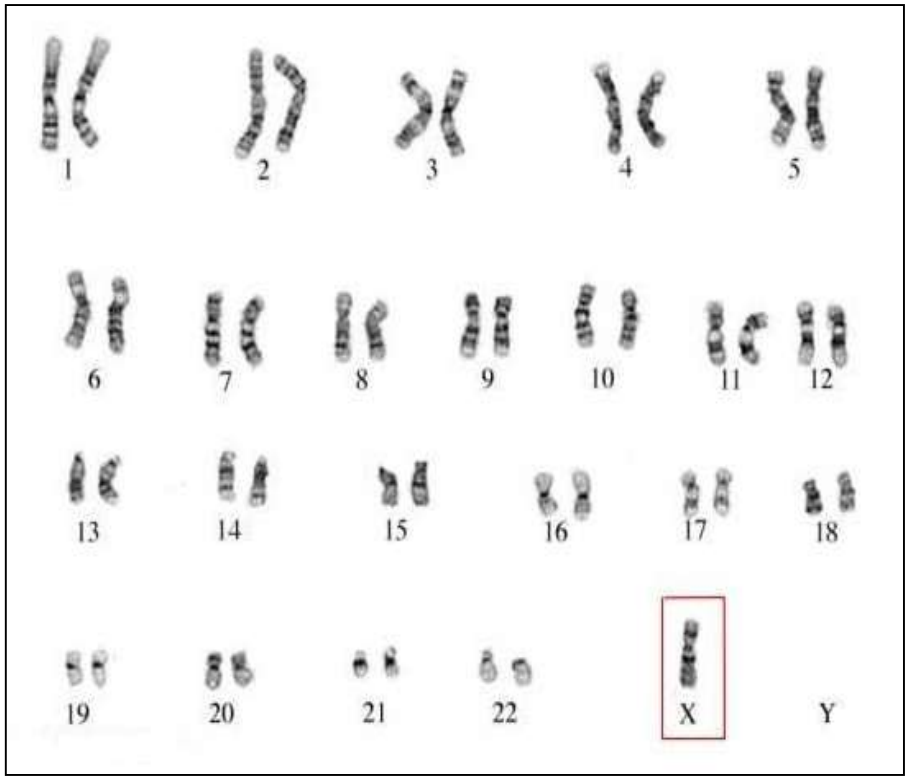
Presence of an extra chromosome, the total number of chromosomes is 47 in a somatic cell.

Trisomy usually results from meiotic non-disjunction



There are 3 of number 21 chromosomes

Monosomy



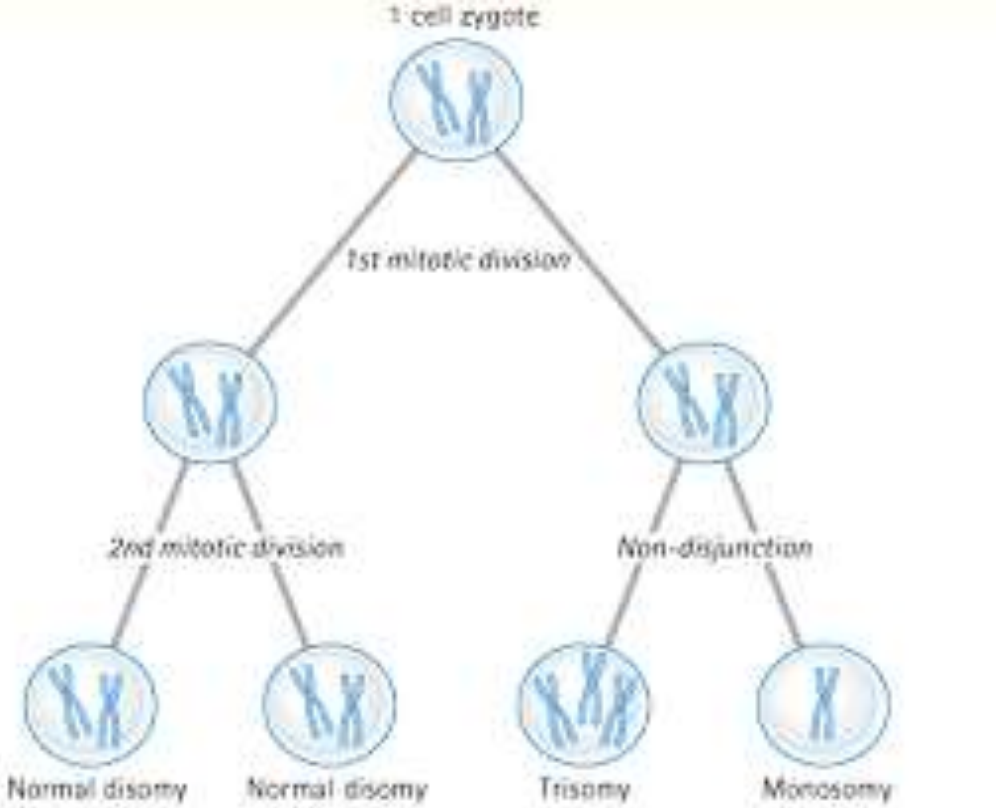
- Absence of one chromosome, so the total number of chromosomes is 45 chromosomes in a somatic cell.
- Usually only seen as 45,X, (autosomal monosomy is usually lethal).
- Monosomy usually results from meiotic non-disjunction.

Mosaicism

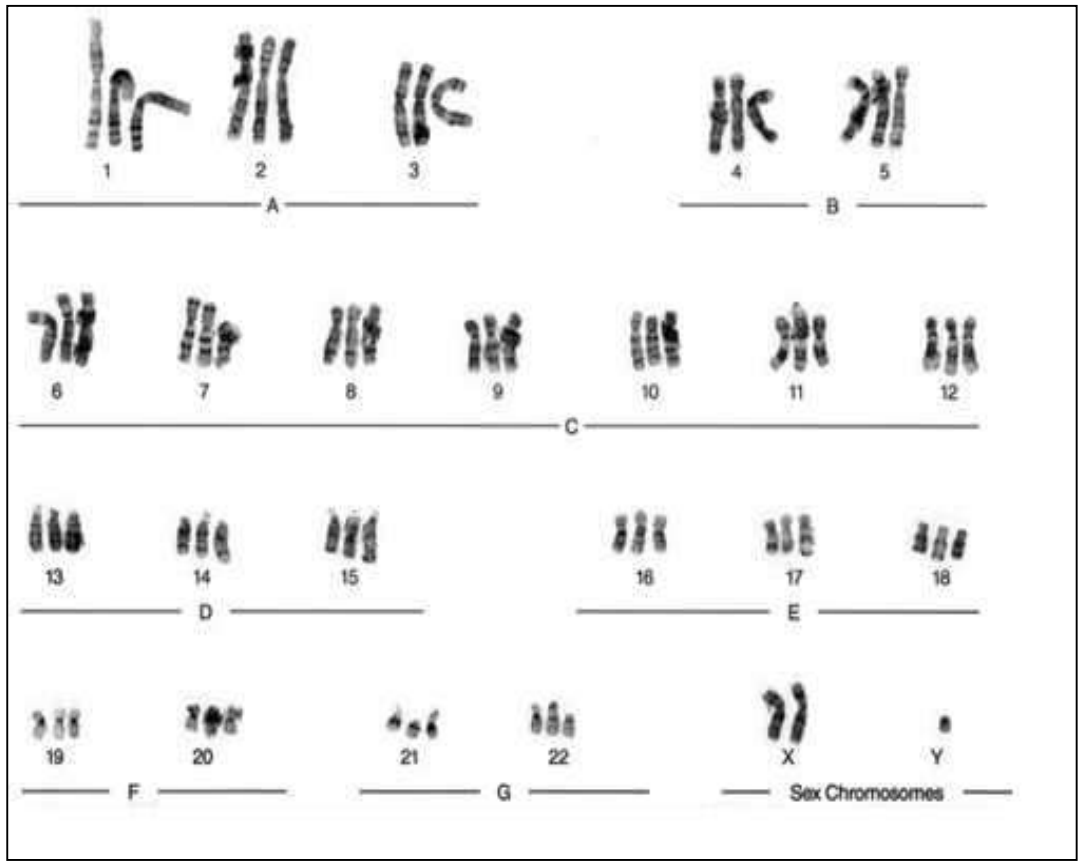
There are 2 types of cells in an individual,

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

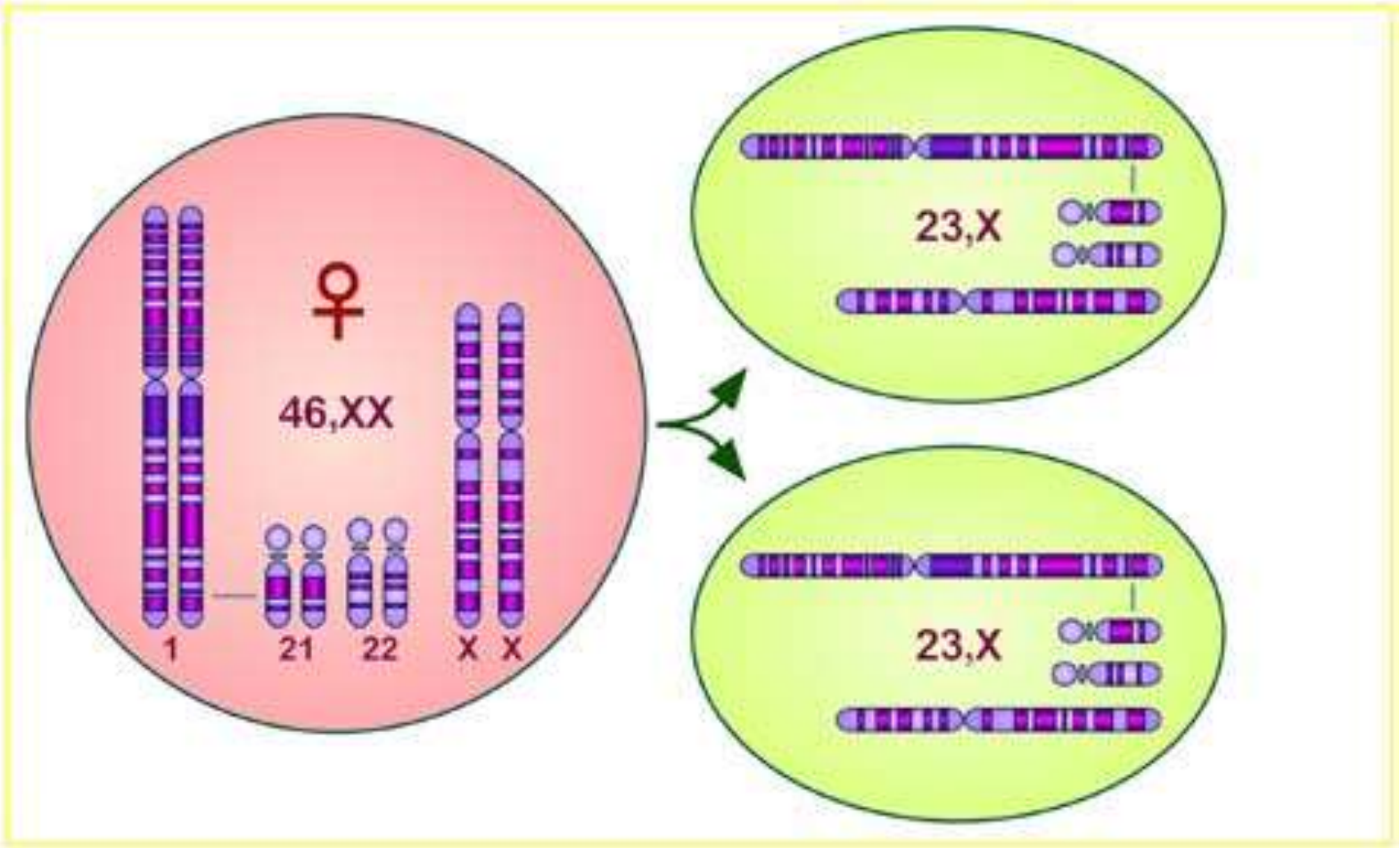


Triploidy

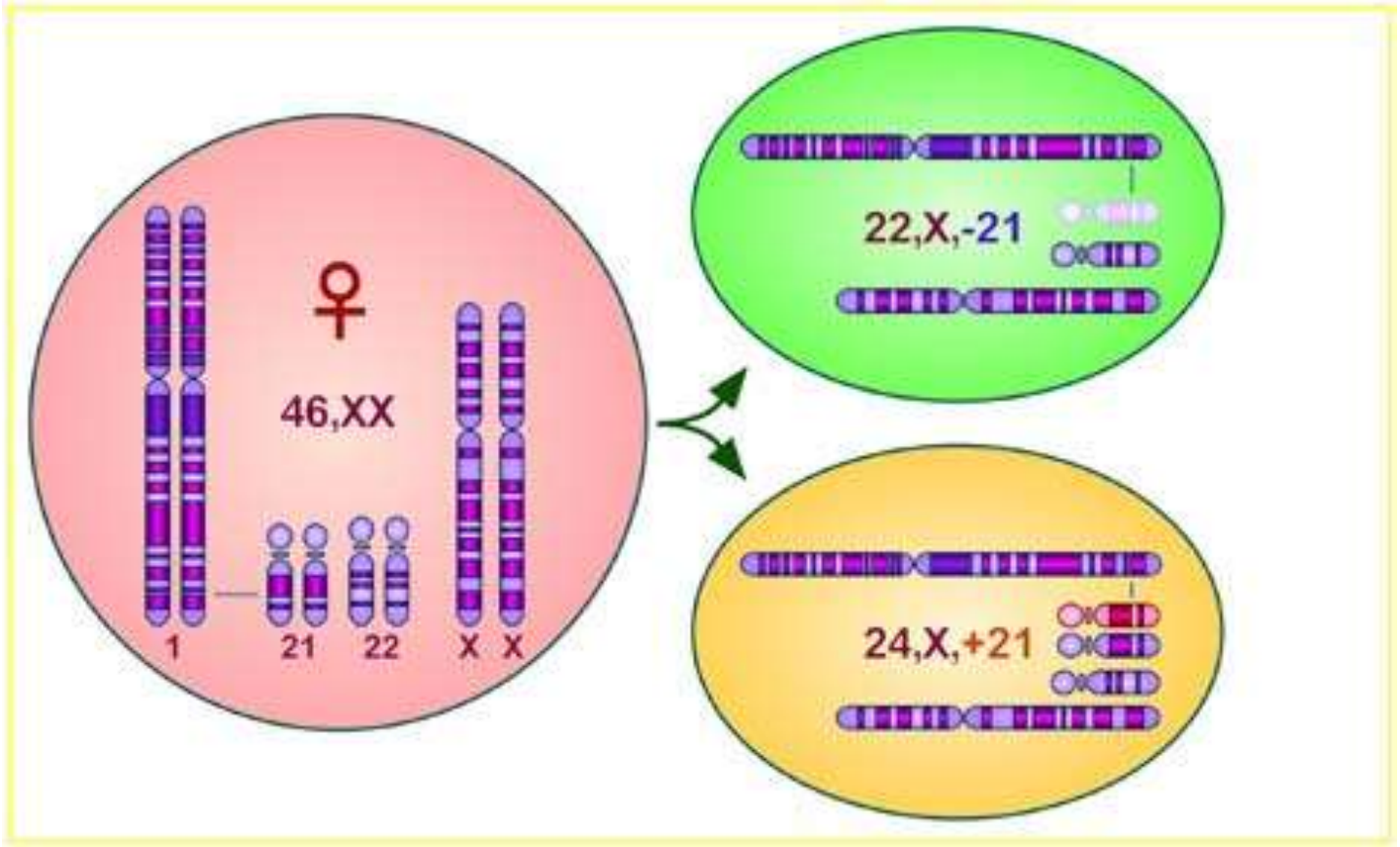


- Presence of 3 haploid sets: 23 x 3= 69 chromosomes
- (haploid set =23, diploid set =46)
- Usually incompatible with life and seen only in abortions.
- May results from 2 sperms fertilizing the ovum or retention of the polar body with the ovum

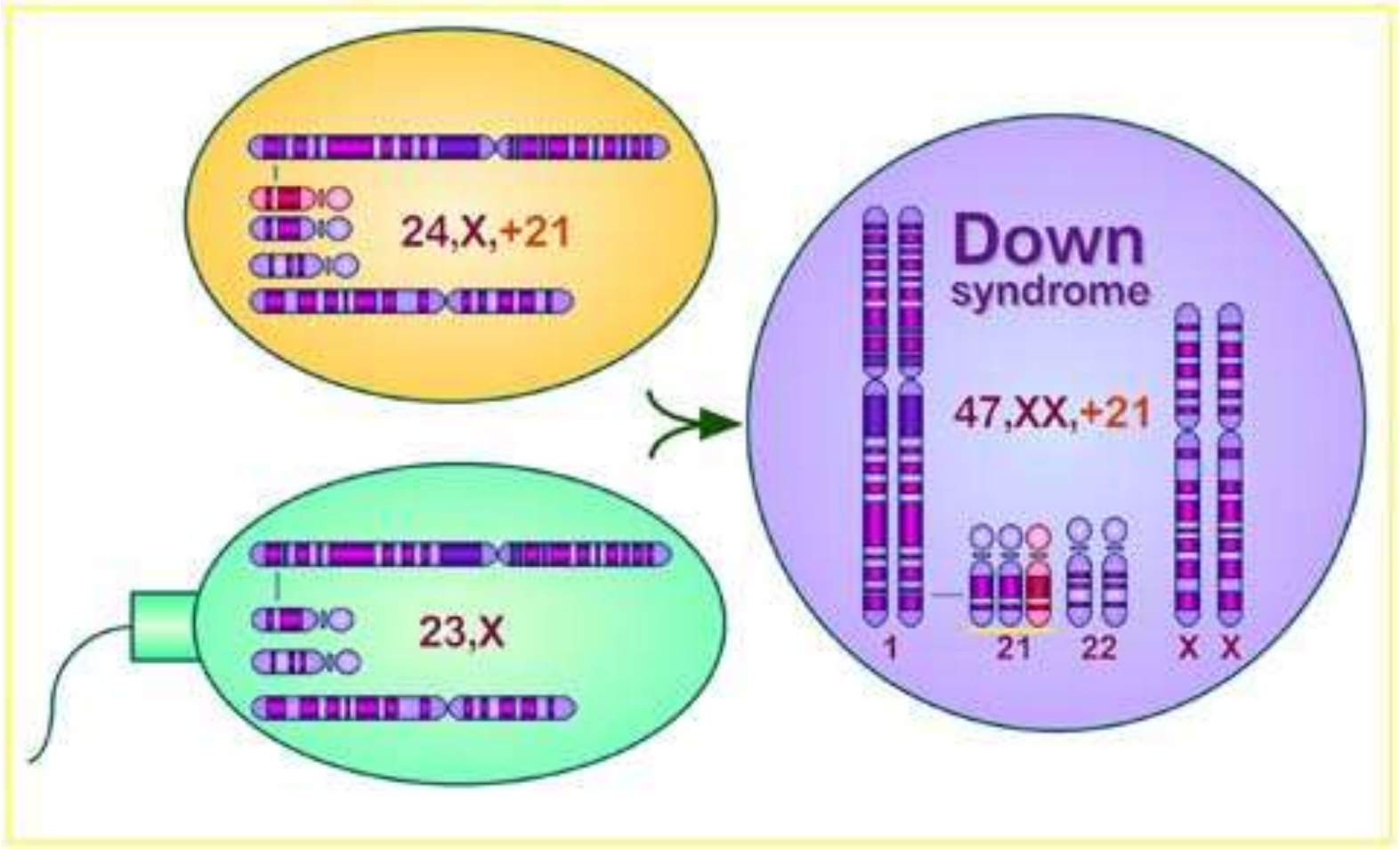
Normal meiosis, the 46 chromosomes become 23 in each gamete



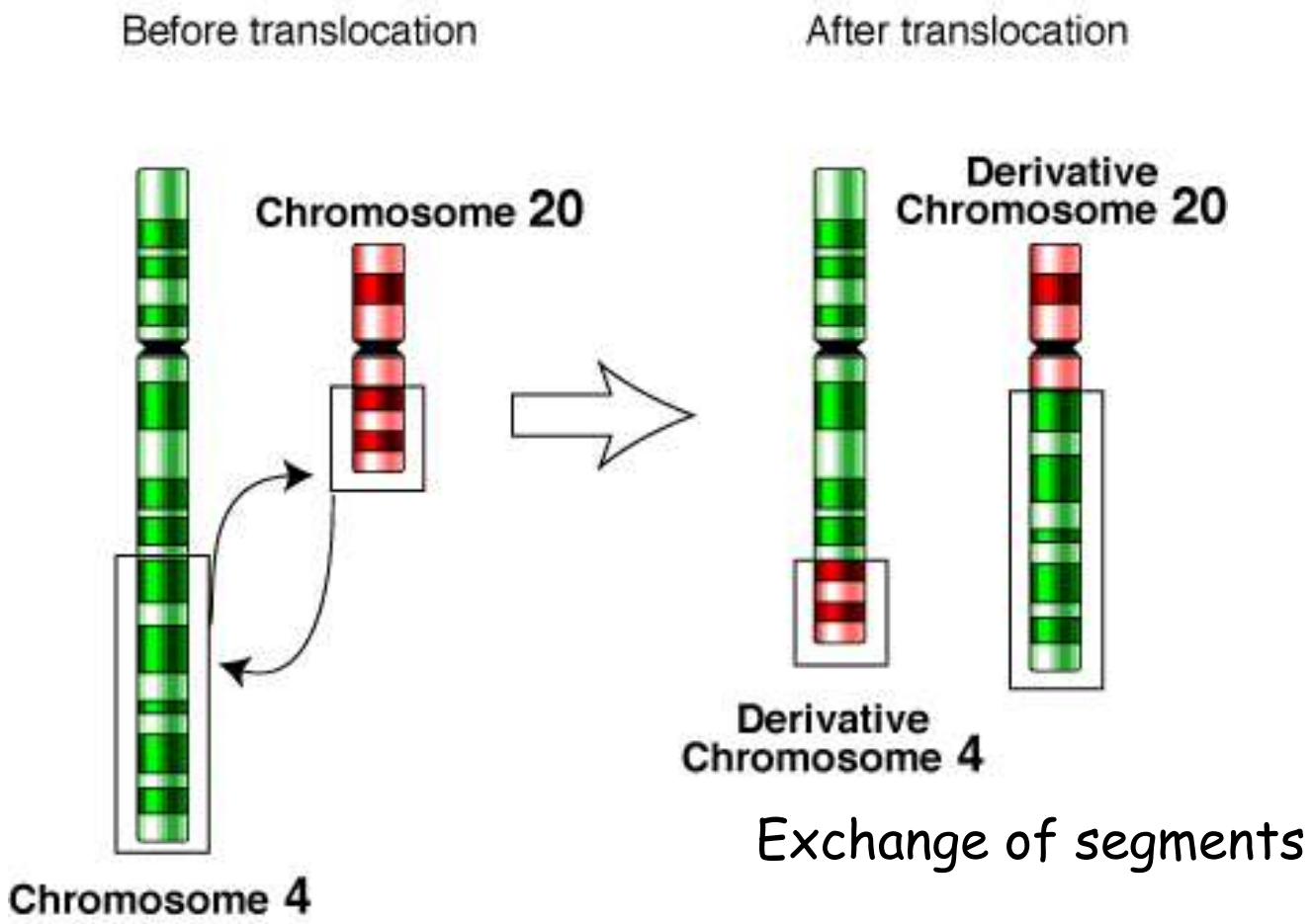
Non-disjunction during meiosis means that one daughter cell gets 24 chromosomes and the other 22 chromosomes



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)

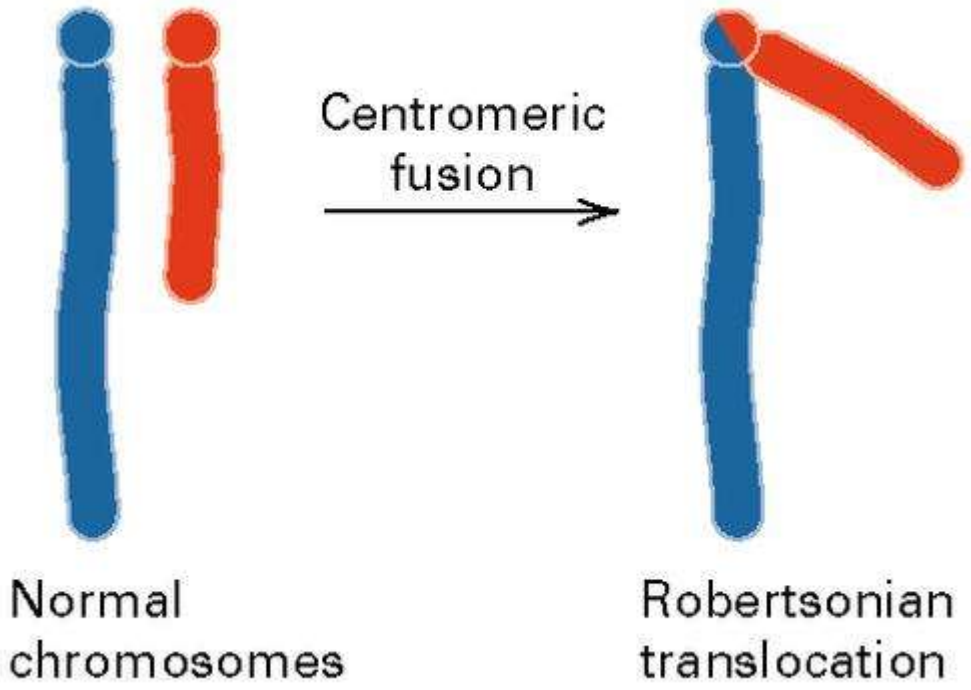


Reciprocal translocation =
exchange of segments between 2 non-homologous chromosomes



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:

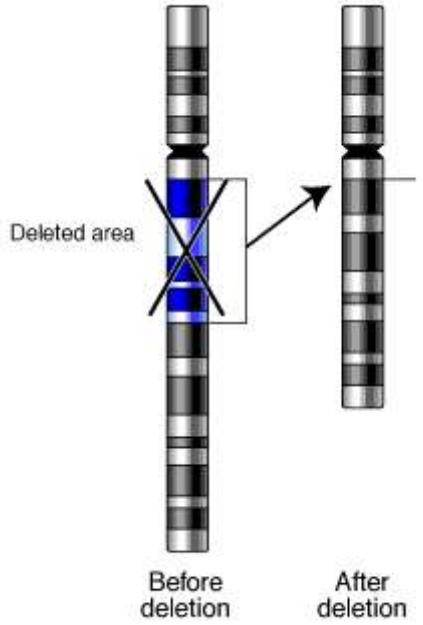
❖ Repeated spontaneous abortions

❖ Stillbirths

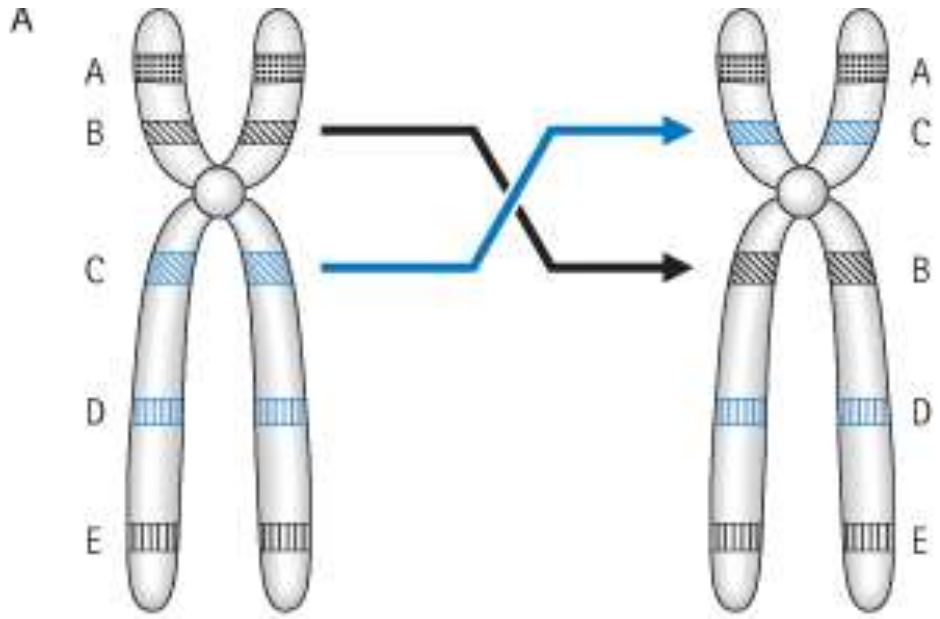
❖ Birth defects

❖ Intellectual disability

Deletion: loss of part of a chromosome



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



Karyotype description

- 46,XX normal female karyotype
- 46,XY normal male karyotype
- 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 chromosome 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)

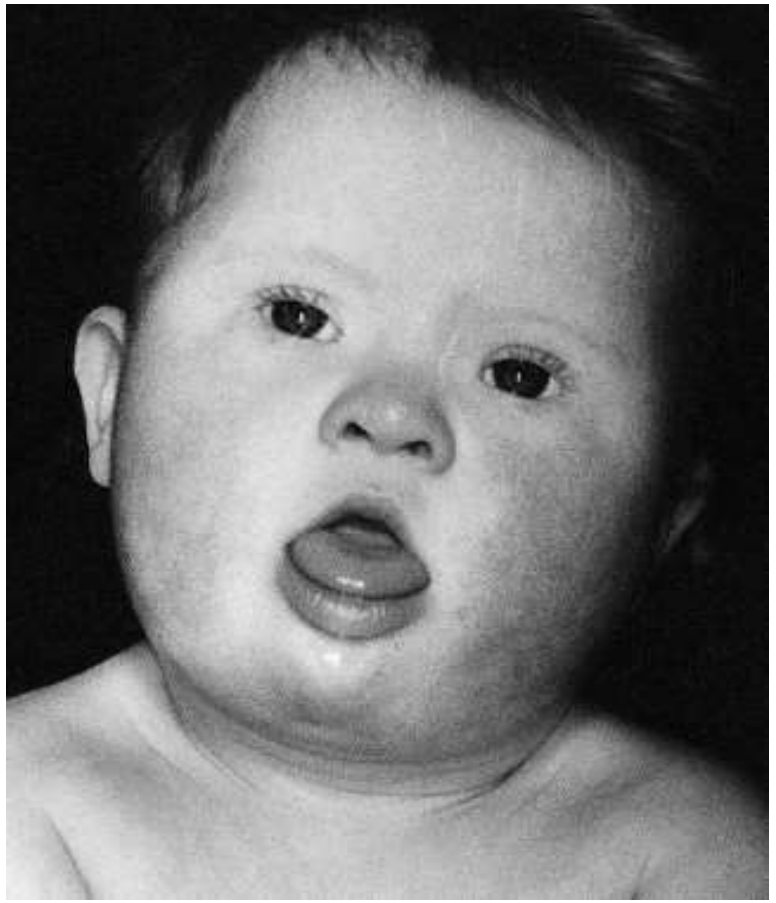
- The overall prevalence at birth is approximately 1 in 650 to 1 in 700 births
- May be higher in some countries where women continue to bear children at an advanced age

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
- brushfield spots and bilateral epicanthic folds.
- small ears
- protruding tongue



Natural history of DS

- Affected children show a broad range of intellectual disability 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 150cm.
- 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.

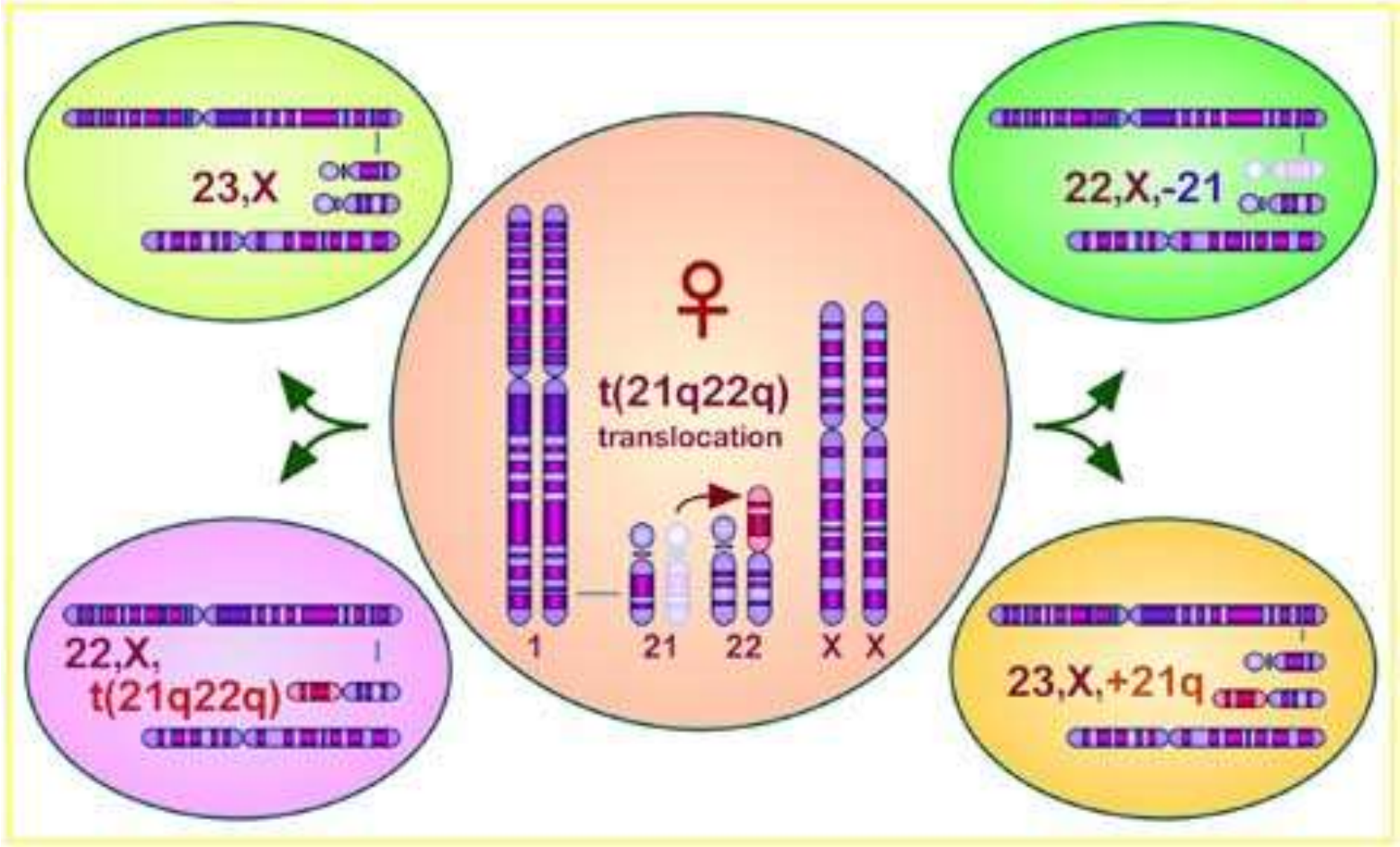
Chromosome abnormalities in Down syndrome

- 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).

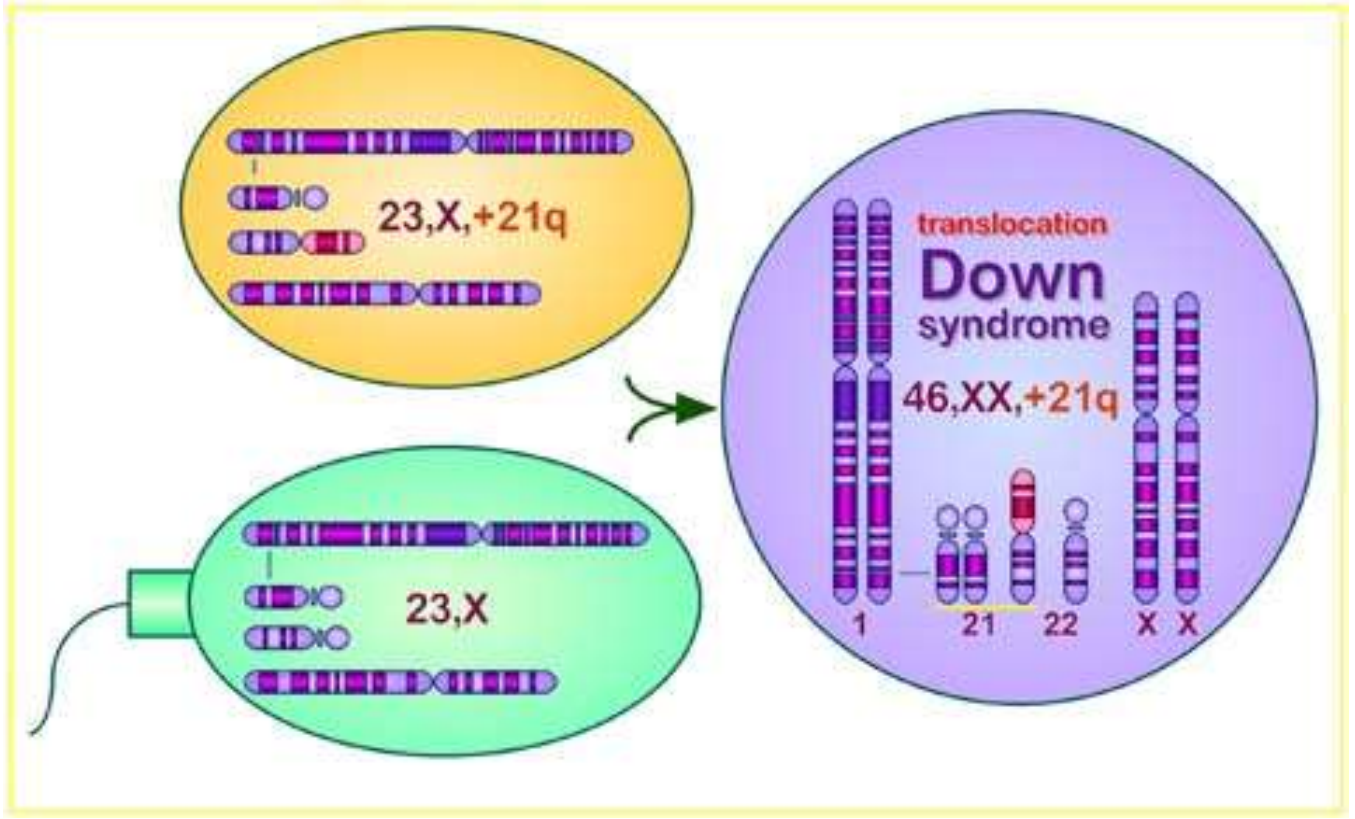
Risk of Down's Syndrome and Chromosomal Abnormalities at Live Birth, According to Maternal Age.		
Maternal Age at Delivery (yr)	Risk of Down's Syndrome	Risk of Any Chromosomal Abnormality
20	1/1667	1/526
25	1/1200	1/476
30	1/952	1/385
35	1/378	1/192
40	1/106	1/66
45	1/30	1/21

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

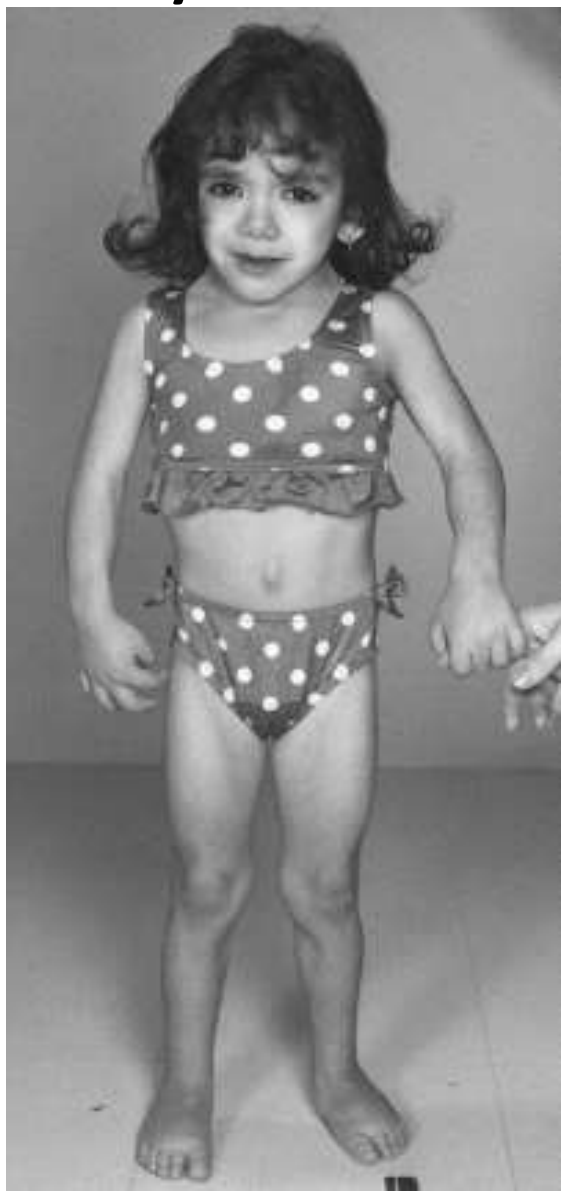


Turner syndrome: monosomy X

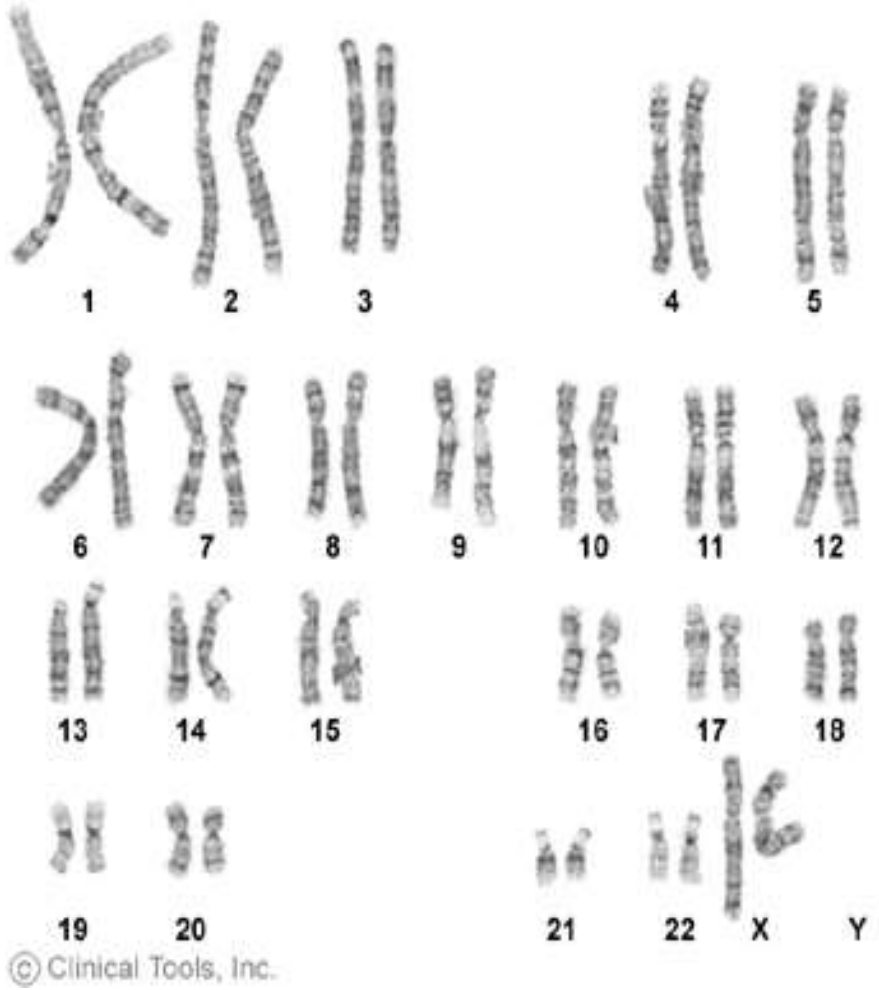
- The two main medical problems are short stature and ovarian failure.

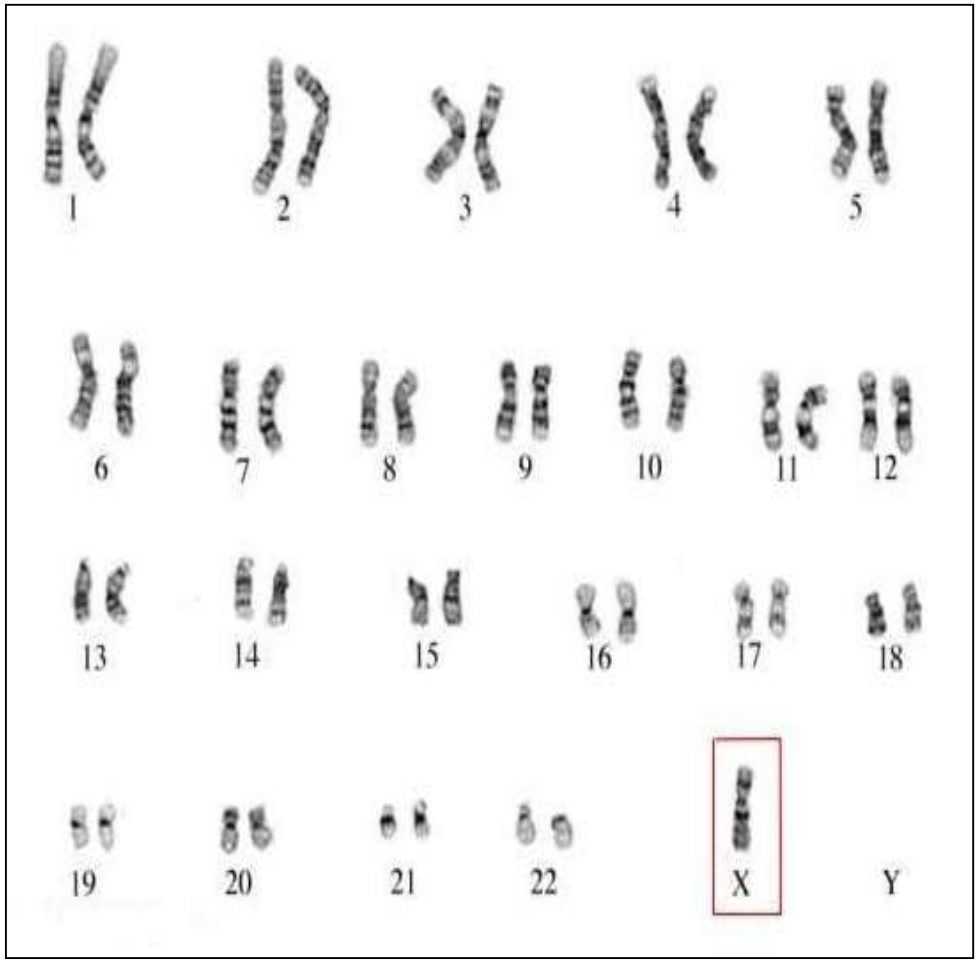
- Ovarian failure leads to primary amenorrhea and infertility.

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

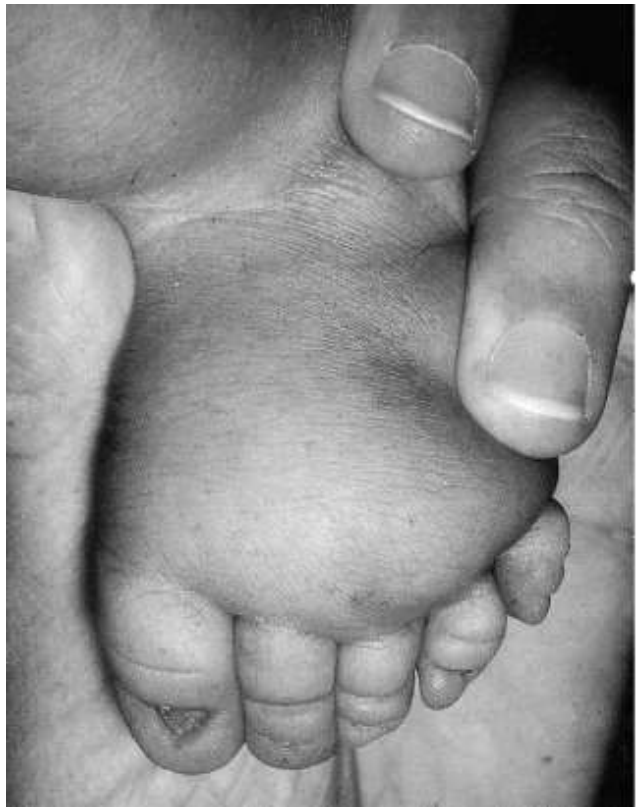


Normal female karyotype and Monosomy X





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) .

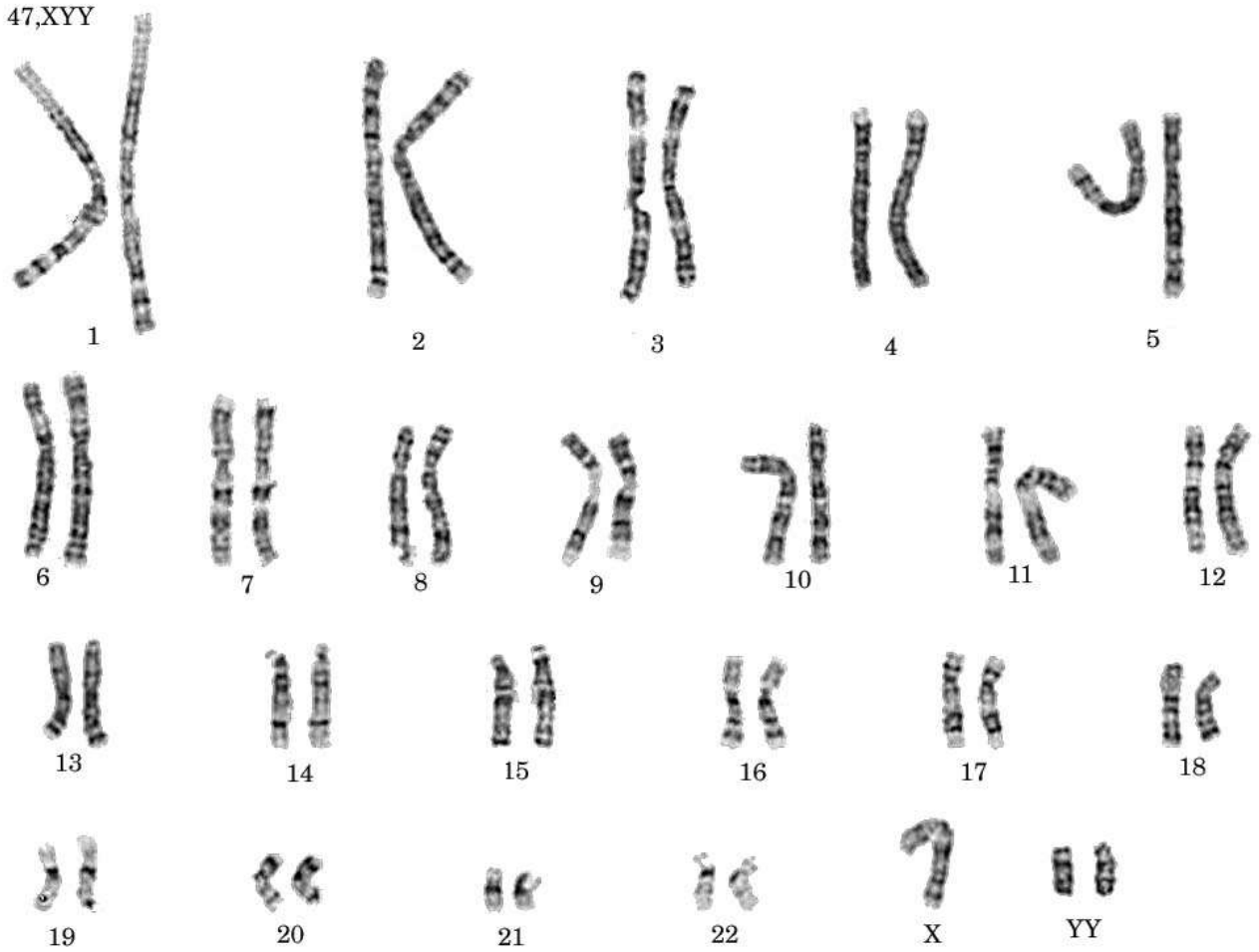
Klinefelter syndrome: 47,XXY

- 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

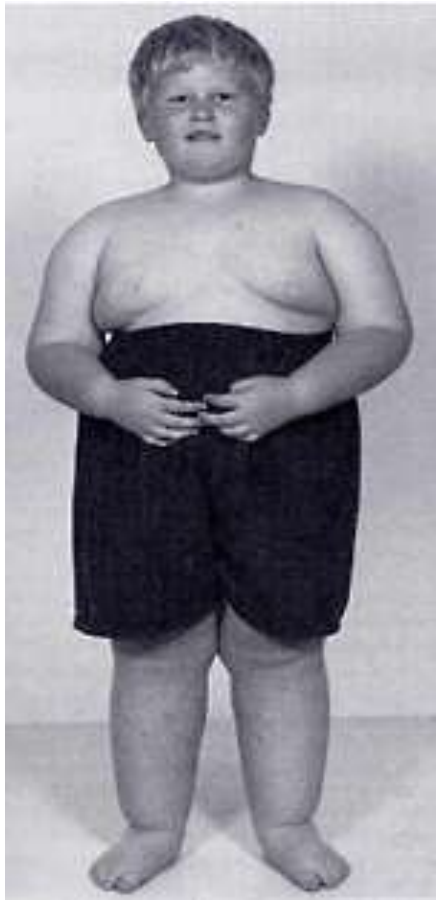
- Fertility is normal.
- Physical appearance is normal and stature is usually above average.
- Intelligence is mildly impaired, with an overall IQ score of 10-20 points below a control sample.
- The additional Y chromosome must arise as a result of non-disjunction in paternal meiosis II or as a post-zygotic 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 and narrow bifrontal diameter
- Hyperthermia
- Gestational History of diminished fetal movements
- Hyperphagia and Obesity
- Short stature
- Small hands and feet
- Mental subnormality
- 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 usually cannot be detected in the standard banded karyotype

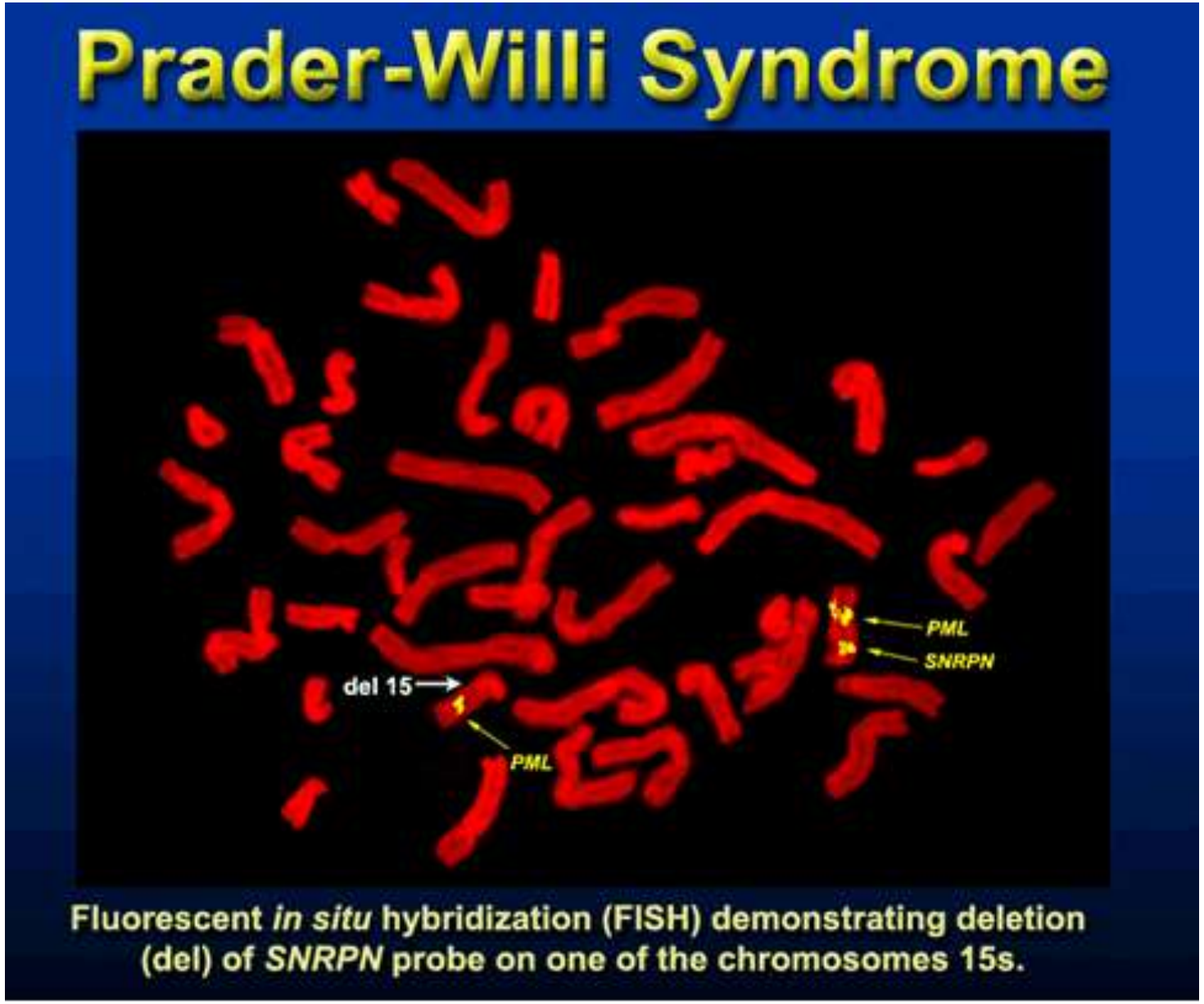

Prader-Willi Syndrome
del 15
PML
PML
SNRPN
Fluorescent *in situ* hybridization (FISH) demonstrating deletion (del) of *SNRPN* probe on one of the chromosomes 15s.

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 in 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