TURNER SYNDROME
HOW TO REQUEST LAB. TESTS

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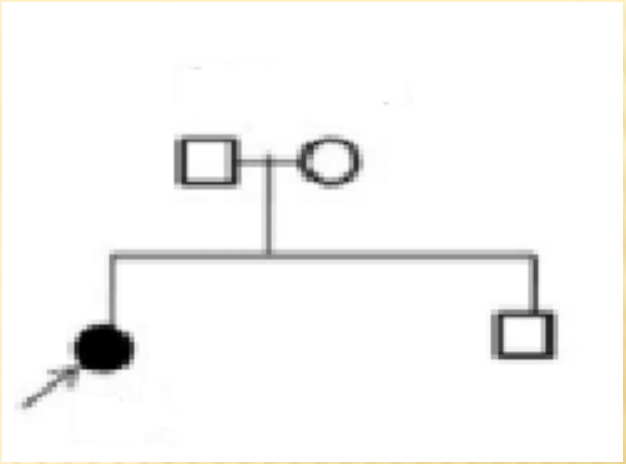
GENETIC DEFINITION OF TURNER SYNDROME

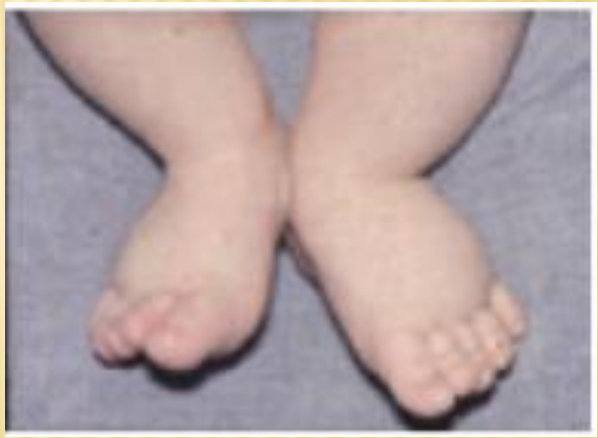
Complete or Partial Loss of One (X) Chromosome

WHO REQUEST LAB. TESTS FOR TURNER

- Prenatologists
- Pediatricians
- Endocrinologists
- Cardiologists
- Orthopedists
- Dermatologist
- Urologist
- Every Physicians

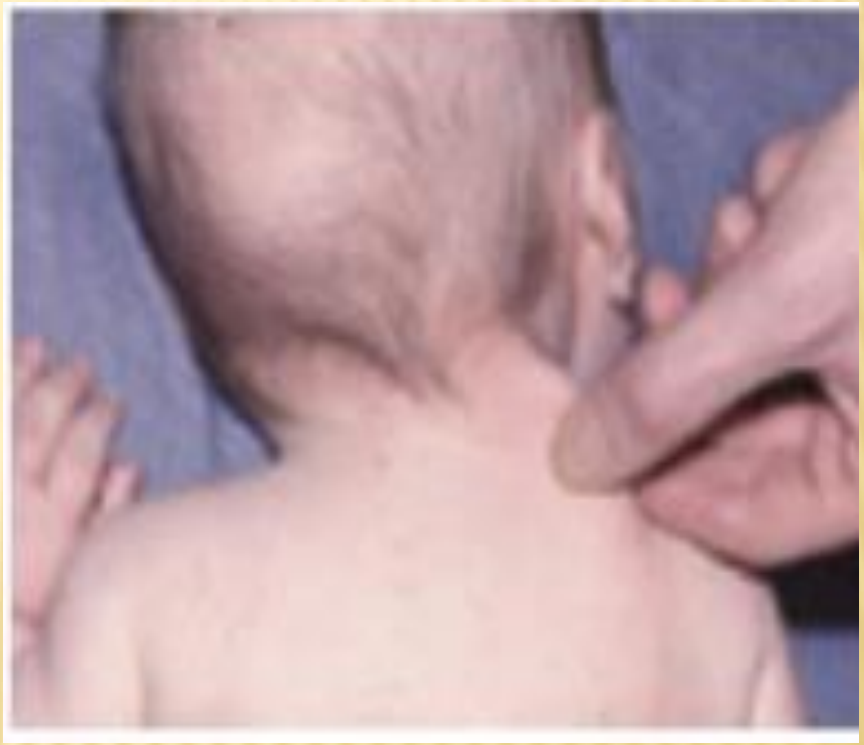
Sara is a 9 months petite girl with good health and normal development brought to the clinic for limb swelling





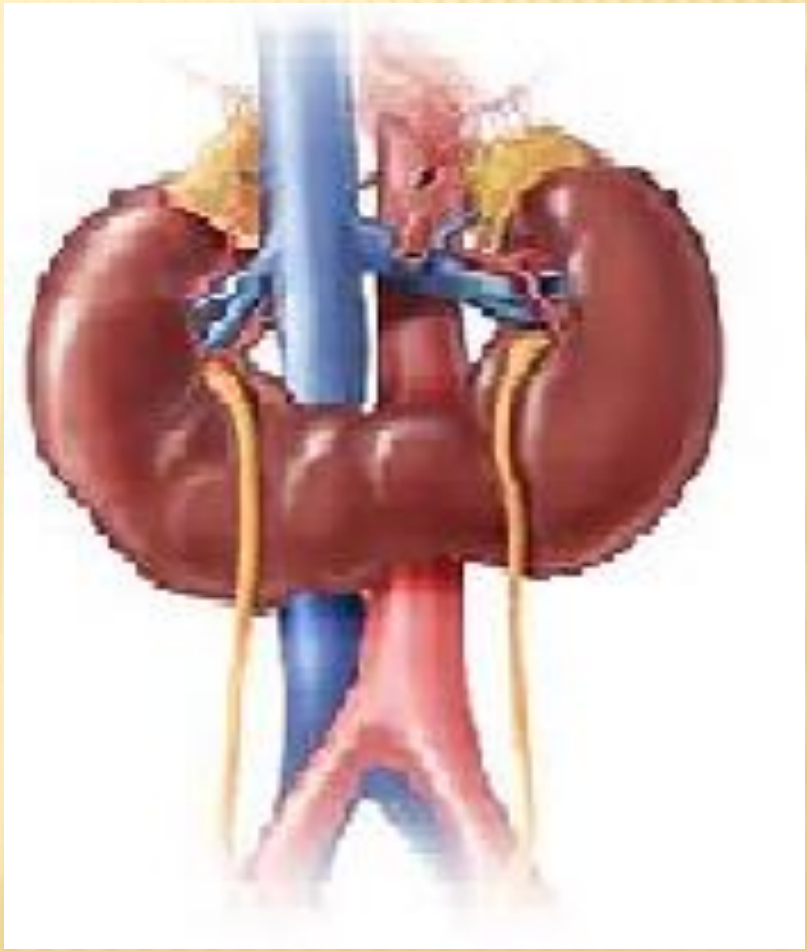
COLLECTION OF UN-RELATED ABNORMALITIES

- Parents also pointed to abnormal redundant skin on the back of her Neck.



ABDOMINAL SONOGRAPHY ORDERED

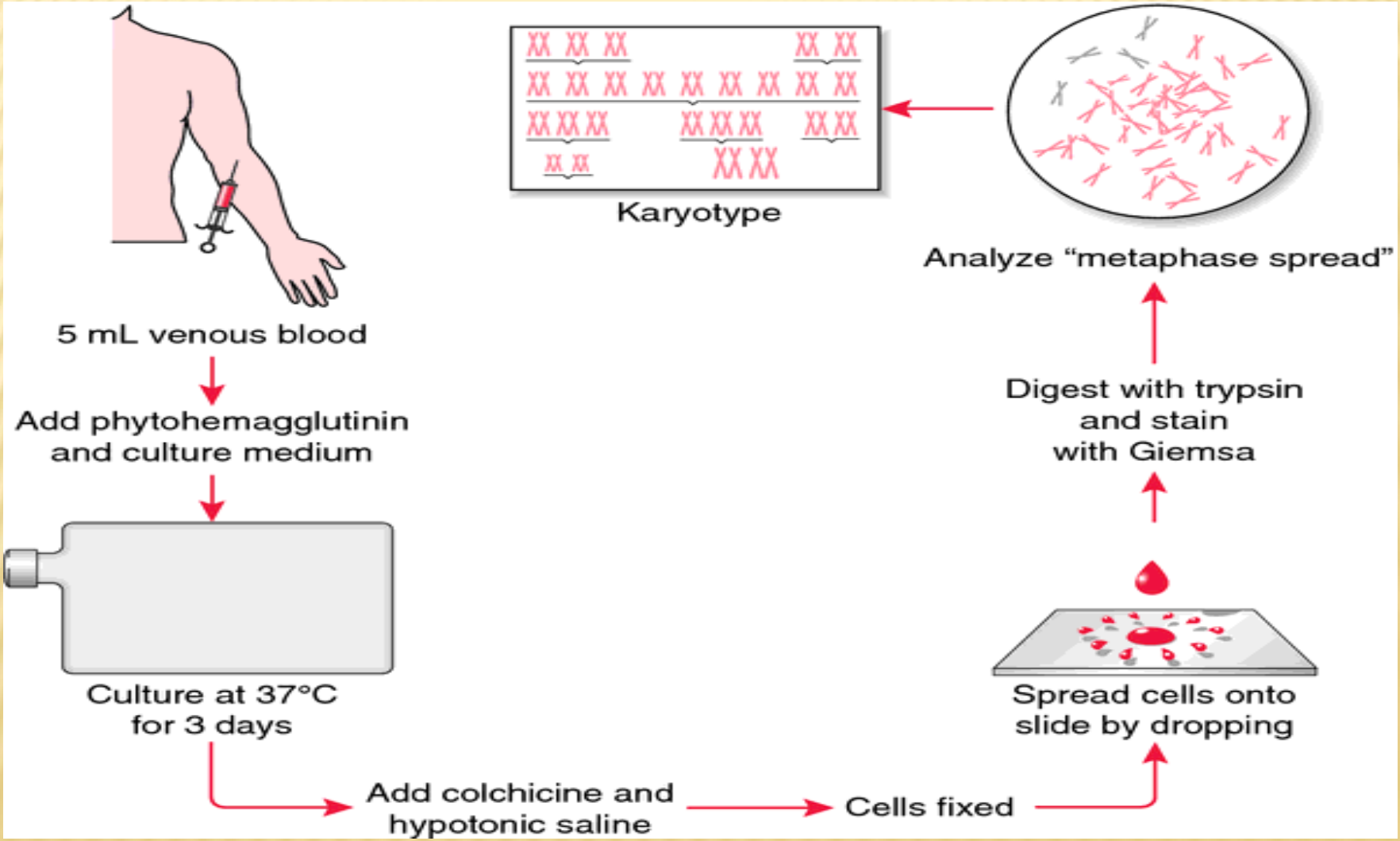
- Horseshoe Kidney Anomaly



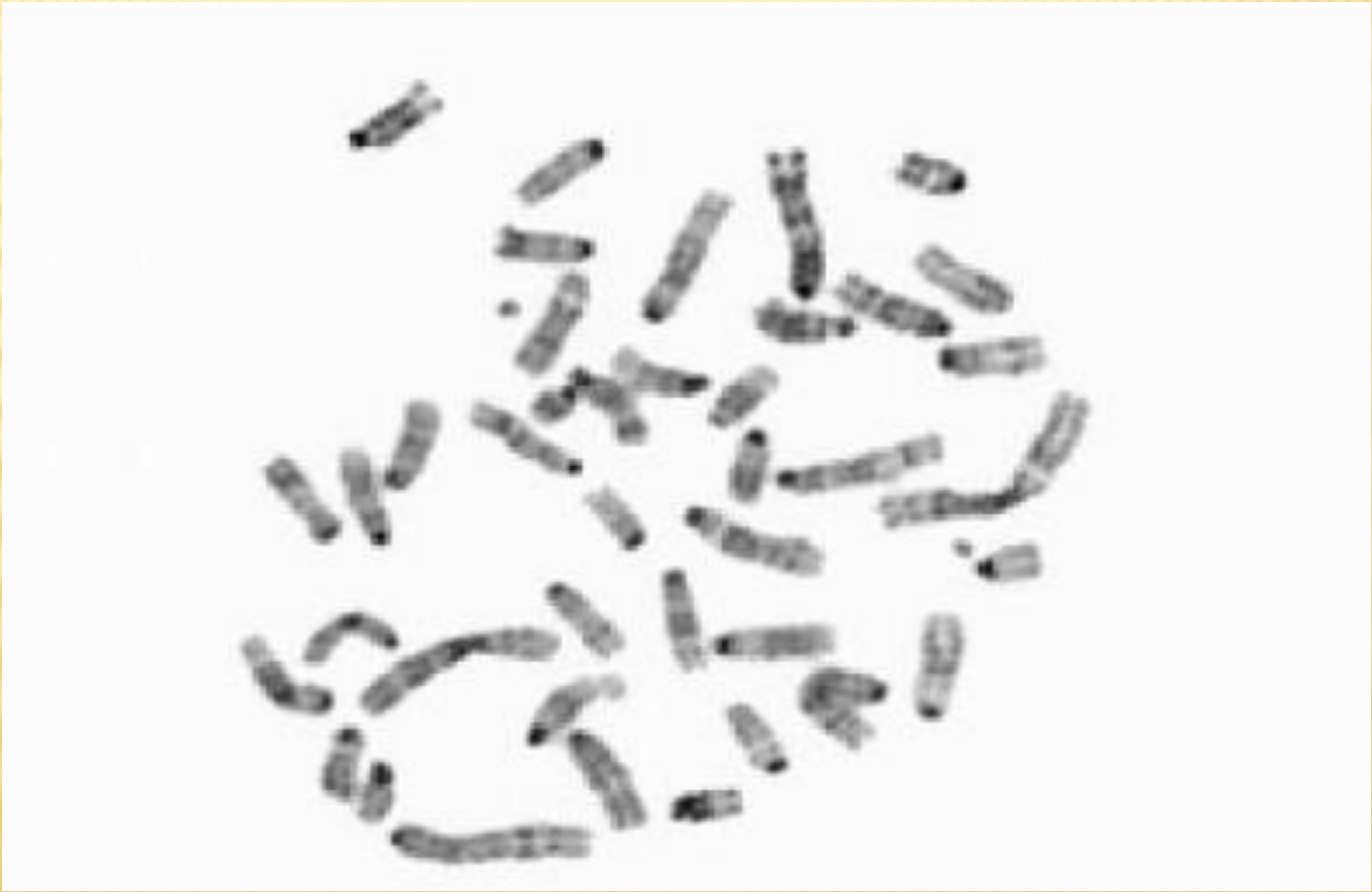
REQUEST BLOOD KARYOTYPE

- Lab please :
  - G Banding Karyotype to R/O Turner Syndrome (Please analysis of 30 metaphase Spreads)
- In routine karyotypes usually the metaphase of 10 or up to 15 cells will be analysed.
- There is a chance to miss low level of mosaicism.
- As reported by Hook, to detect 10% mosaicism with 95% confidence, ≥ 29 metaphases are needed to exclude a mosaic cell line (such as 45,X). To detect 5% and 1% mosaicism with 95% confidence, ≥ 59 and ≥299 metaphases, respectively, are needed

KARYOTYPE PROCEDURE



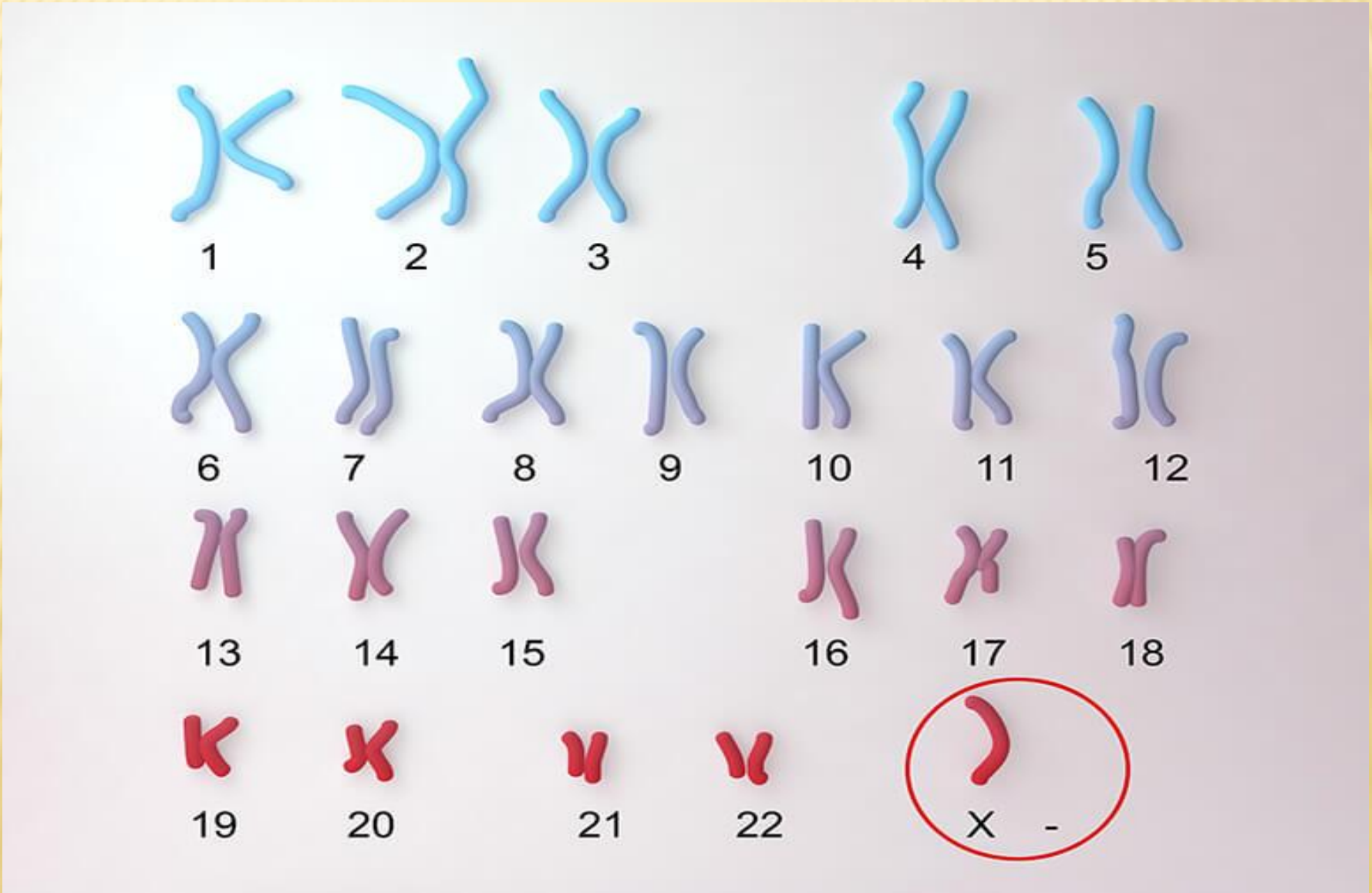
METAPHASE SPREAD



KARYOTYPE PROCEDURE

4 The slide is viewed by a light microscope equipped with a camera; the sample is seen on a computer screen. The chromosomes can be photographed and arranged electronically on the screen.

KARYOTYPE REPORT FOR SARA (45XO)



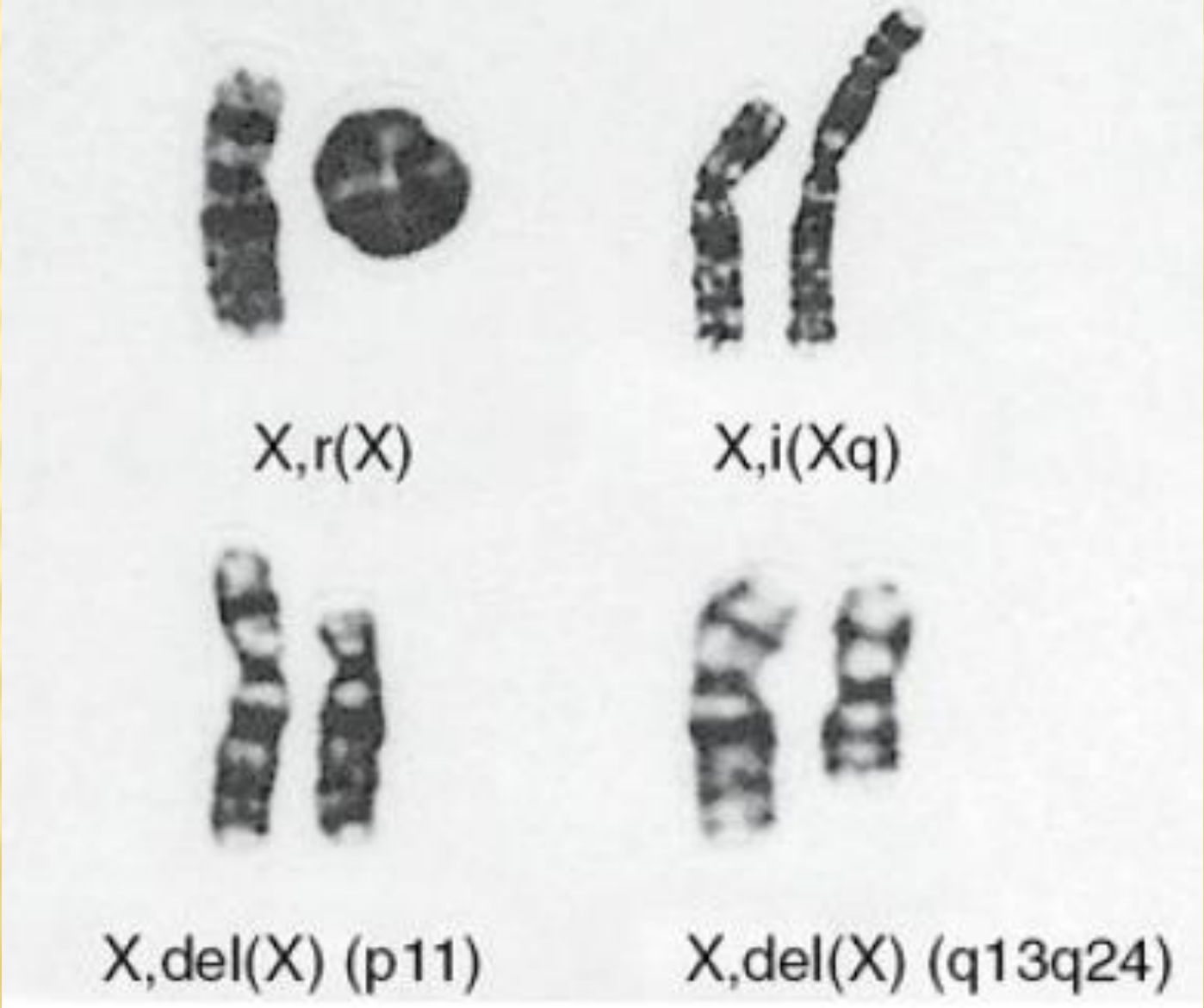
IMPORTANT TERMINOLOGIES IN KARYOTYPE REPORTS RELATED TO TURNER SYNDROME

- 1) Numerical abnormalities(Trisomy-Monosomy)
- 2) Structural abnormalities (Breakage)

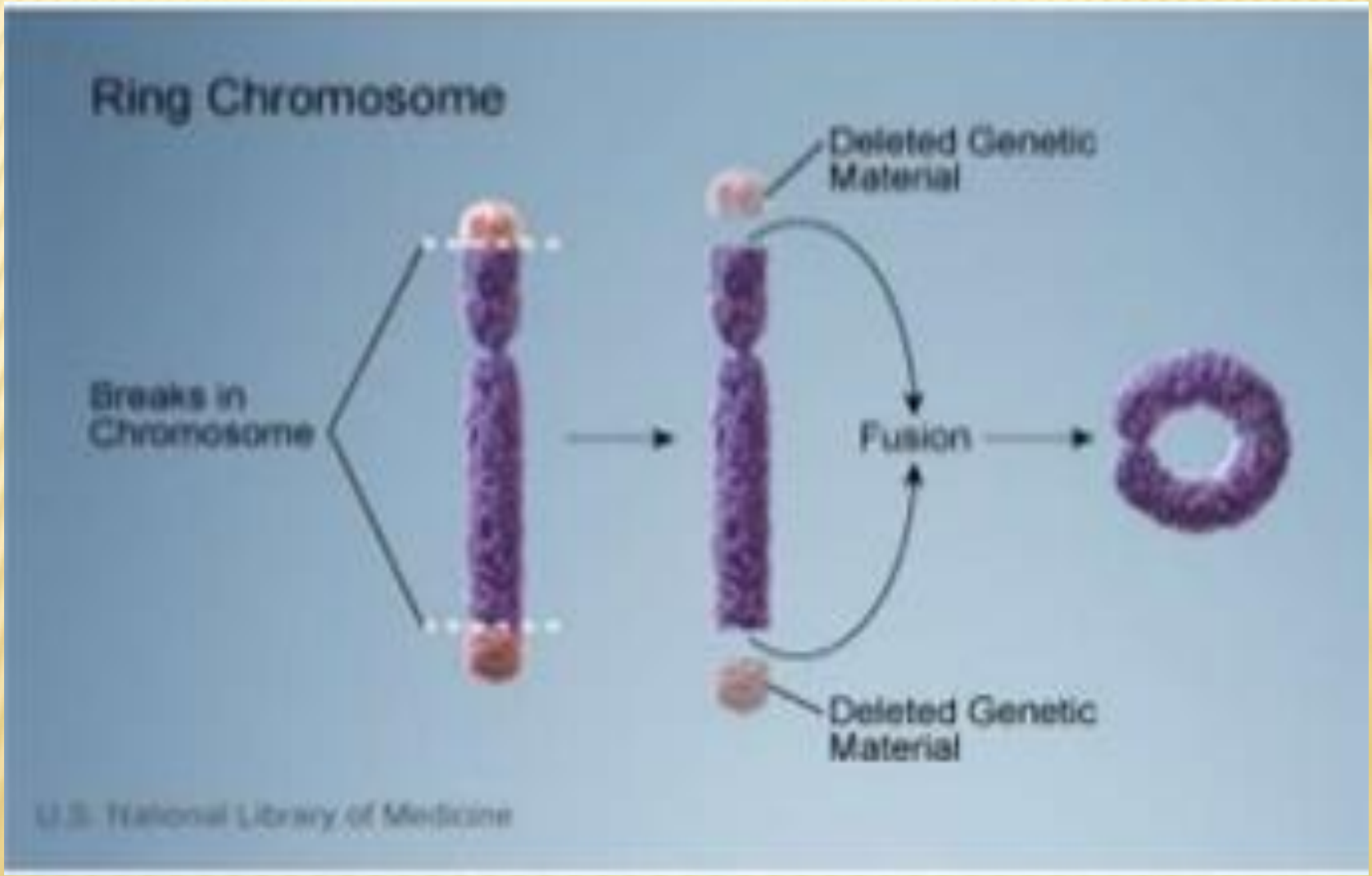
  Abn(X) ; Ring Chromosome ; del (Xp) ; Isochromosome i(Xq)

- 3) Mosaicism

PARTIAL (X) DELETION ABNORMALITIES IN TURNER



ABNORMAL X IS SEEN IN 20% OF TURNERS



CLINICIAN ORDERED A CELL FREE DNA TEST FOR Y CHROMOSOME FOR SARA !!!

METHODS OF (Y) CHROMOSOME DETECTION

- 1) FISH with Probe for SRY
- 2) PCR on cell free DNA for SRY
- 3)FISH probe for DYZ3 (Y centromer)

GENETIC MECHANISMS OF TURNER SYNDROME

WHAT CAUSES TURNER SYNDROME ?

Non-Dysjunction vs Anaphase Lag

PRE-ZYGOTIC VS POSTZYGOTIC ERRORS

GENETIC CLASSIFICATION OF TURNER

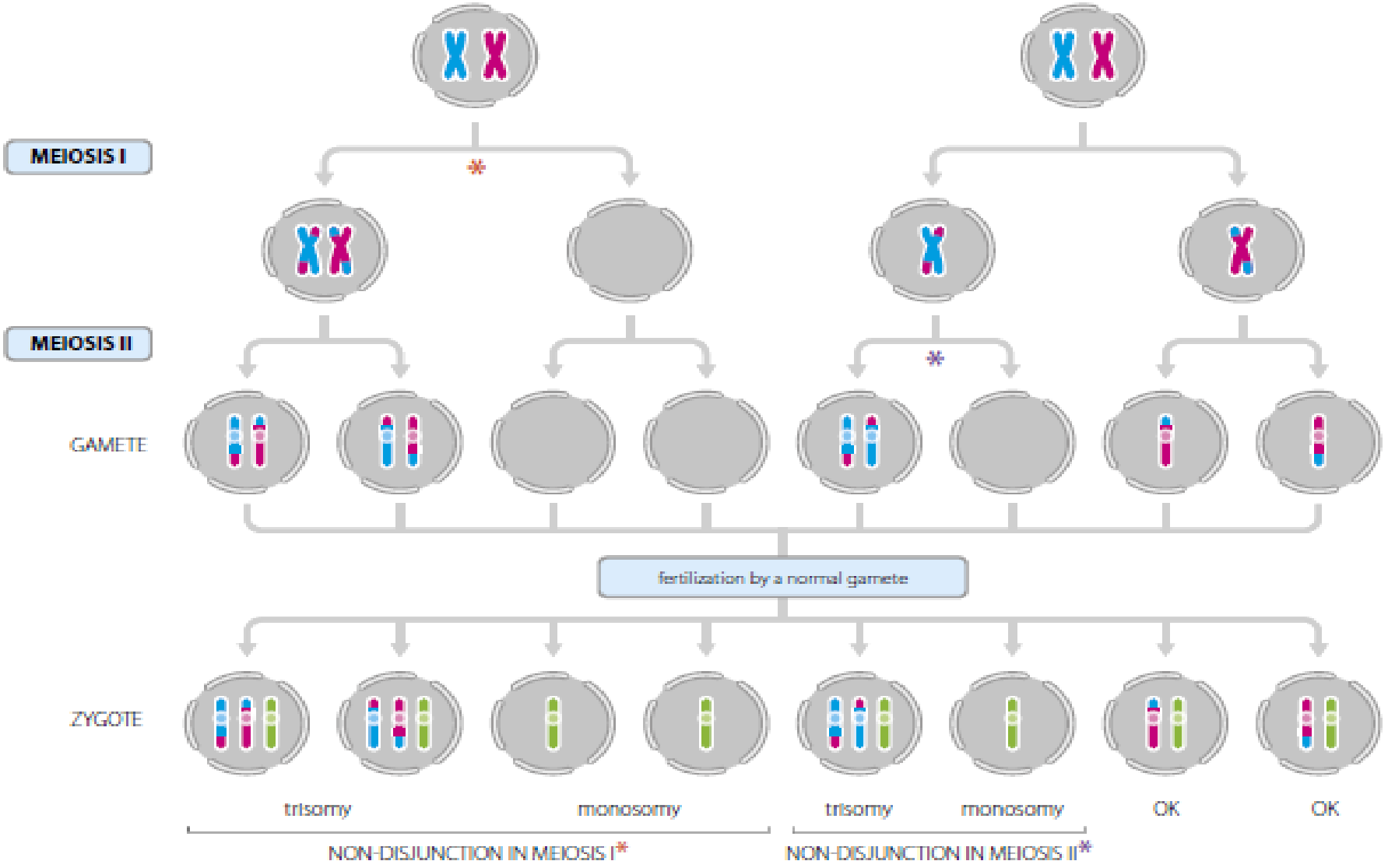
- 1)Simple **Numerica**l abnormality (Monosomy)
- 2) **Structural** X Abnormality (Breackage)

- A) Turner Syndrome **without Mosaicism**
- B) Turner Syndrome **with Mosaicism**

- B1) Mosaic Turner **without Y Chromosome**
- B2) Mosaic Turner **with Y Chromosome**

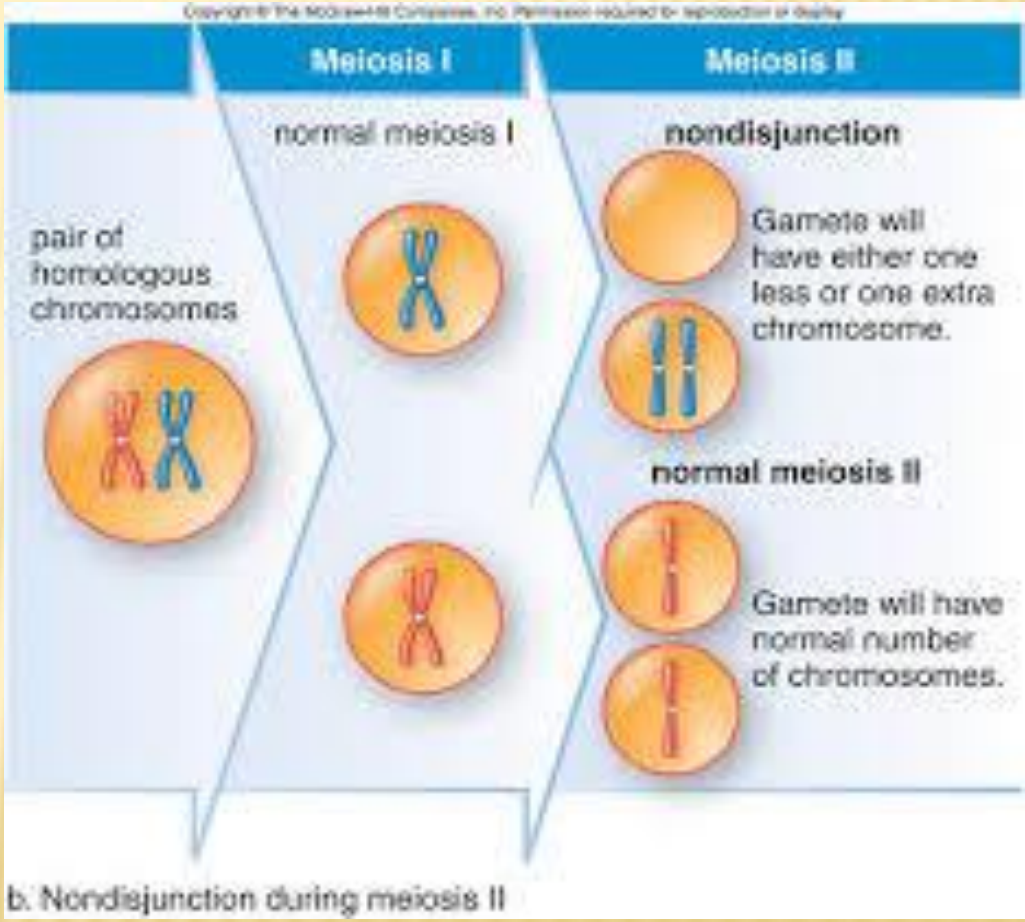
PREZYGOTIC ERROR

NON-DYSJUNCTION IN MEIOSIS



NUMERICAL CHROMOSOMAL ABNORMALITIES PREZYGOTIC ERROR

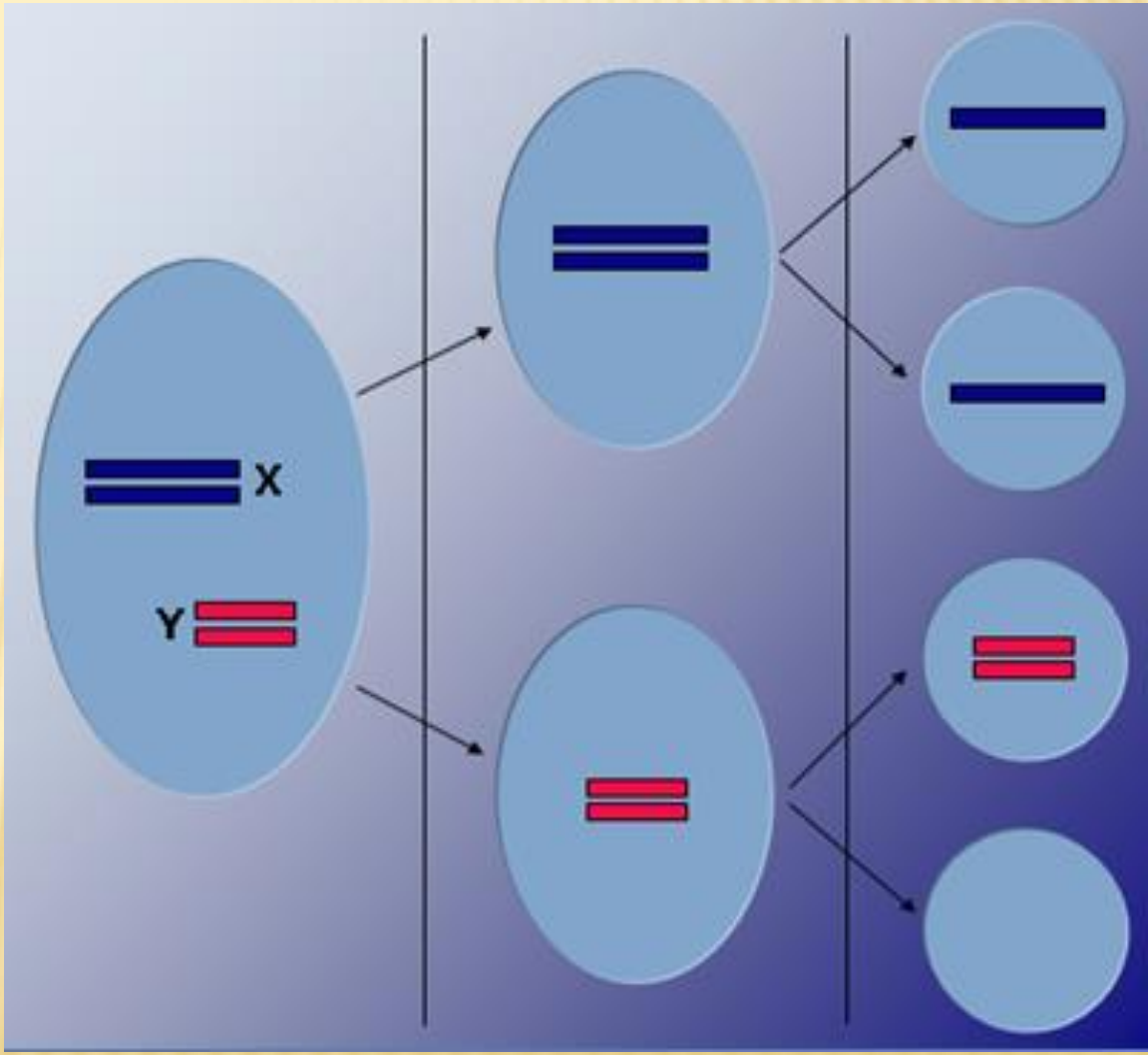
- Most of the chromosomal abnormalities are due to **non-dysjuntion** at the level of Meiosis I or Meiosis II stage.



NON-DYSJUNCTION OF SEX CHROMOSOMES PREZYGOTIC ERROR

- **In male meiosis** the X and Y chromosomes also pair. Although most of their sequence is completely different,there is a short region of homology at the tips of the short arms **pseudoautosomal region,**

the X and Y use this to pair end-to-end.



NON-DYSJUNCTION IN MEIOSIS

- 1) The nondisjunction could happen at either division of meiosis in either parent.
- 2) DNA marker studies showed that 80 % of cases were due to non-disjunction in the meiotic division in the father.
- 3)In other chromosomal aneuploidies ,the phenomenon of non-dysjunction is strongly age dependent with except of Turner syndrome .
- 4) In male meiosis the X and Y chromosomes also pair. Although most of their sequence is completely different,there is a short region of homology at the tips of the short arms (the **pseudoautosomal region,** ***and the X and Y use this to pair end-to-end.***

SEX CHROMOSOME ANOMALY

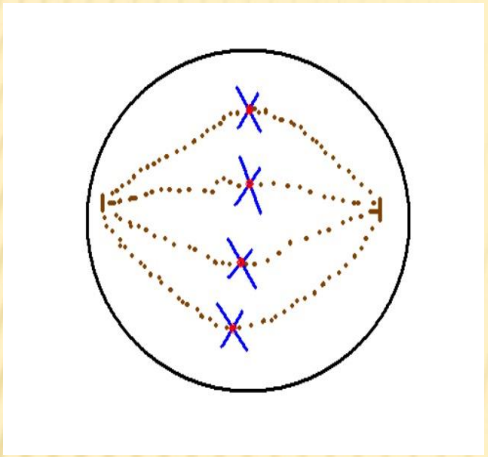
- Turner is the only human monosomy that is not lethal early in development. Because males survive with only one X chromosome, maybe it is not surprising that Turner syndrome is not always lethal. But in fact it is lethal in over 90% of prenatal cases.
- Fetuses with Turner syndrome can be grossly distended with fluid and the great majority abort spontaneously.

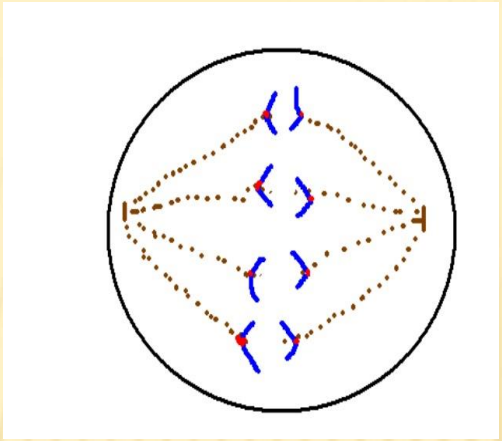
KARYOTYPE OF SARA ; 45XO
TRULY NON-DYSJUNCTION ??

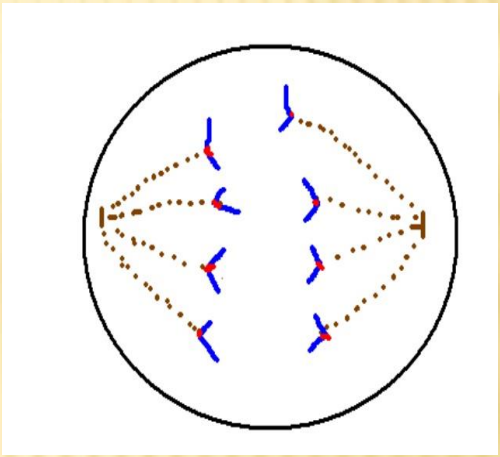
MAIN GENETIC MECHANISM IN TURNER IS ANAPHASE LAG

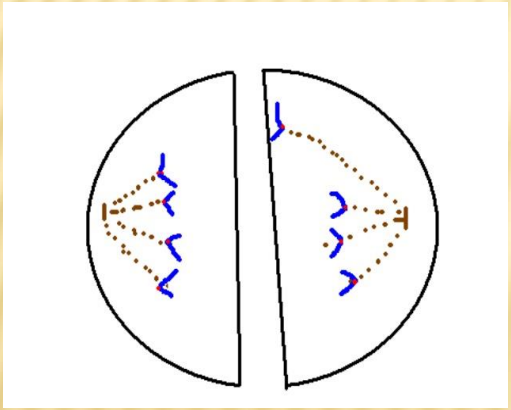
- Unlike all the trisomies, the risk of Turner syndrome does not increase with maternal age.
- The mechanism is different. Rather than non-disjunction, Turner syndrome is the result of anaphase lag, in which one of the sex chromosomes moves too slowly to the pole of a daughter cell during cell division, and ends up outside the nucleus, where upon it is broken down.
- It can arise after conception during an early mitotic division. Many Turner women are mosaics.

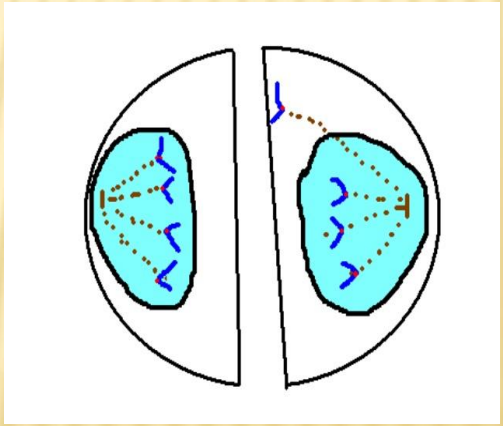
POSTZYGOTIC ERROR ANAPHASE LAG

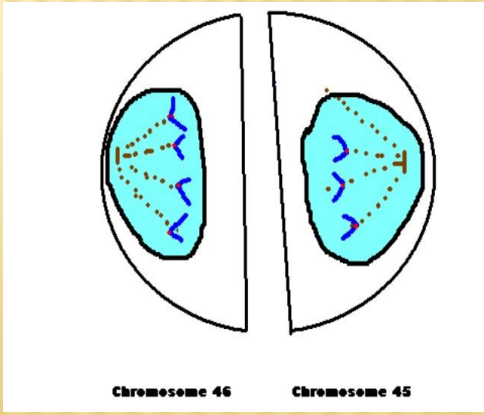




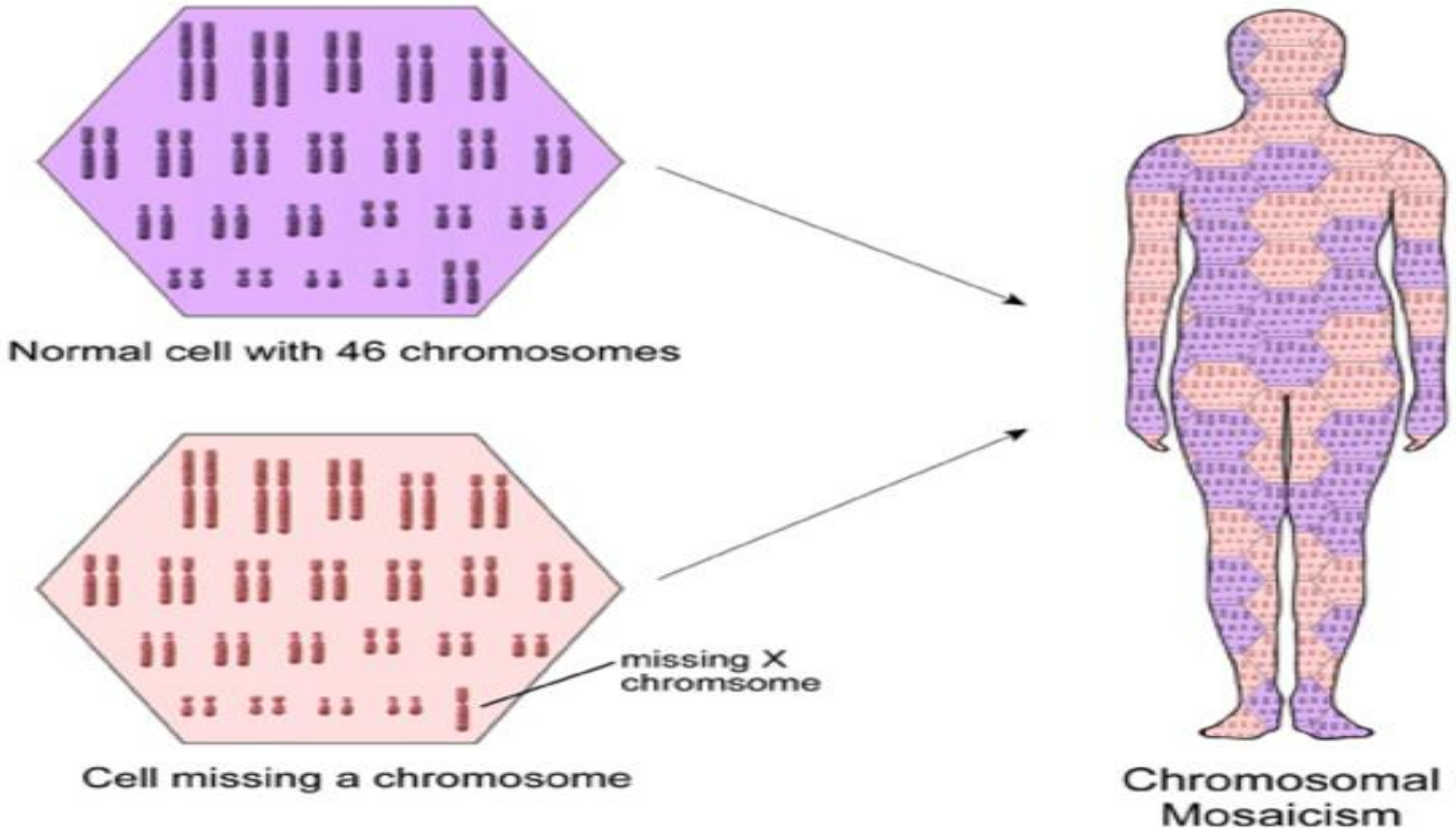








MOSAIC TURNER SYNDROME



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MOSAICISM

- Chromosomal abnormalities may be constitutional (present in all cells) or in mosaic form (present in a subset of cells)
- Every chromosal abnormality may occur in post-zygotic stage due to mitosis errors.
- Many abnormalities that would be lethal if present in constitutional form can survive in mosaics. For example, a patient may have mosaic trisomy 8, but is unlikely to have full constitutional trisomy 8.

GENOTYPIC CLASSIFICATION OF TURNER

Sexual development and differentiation in Turner Syndrome

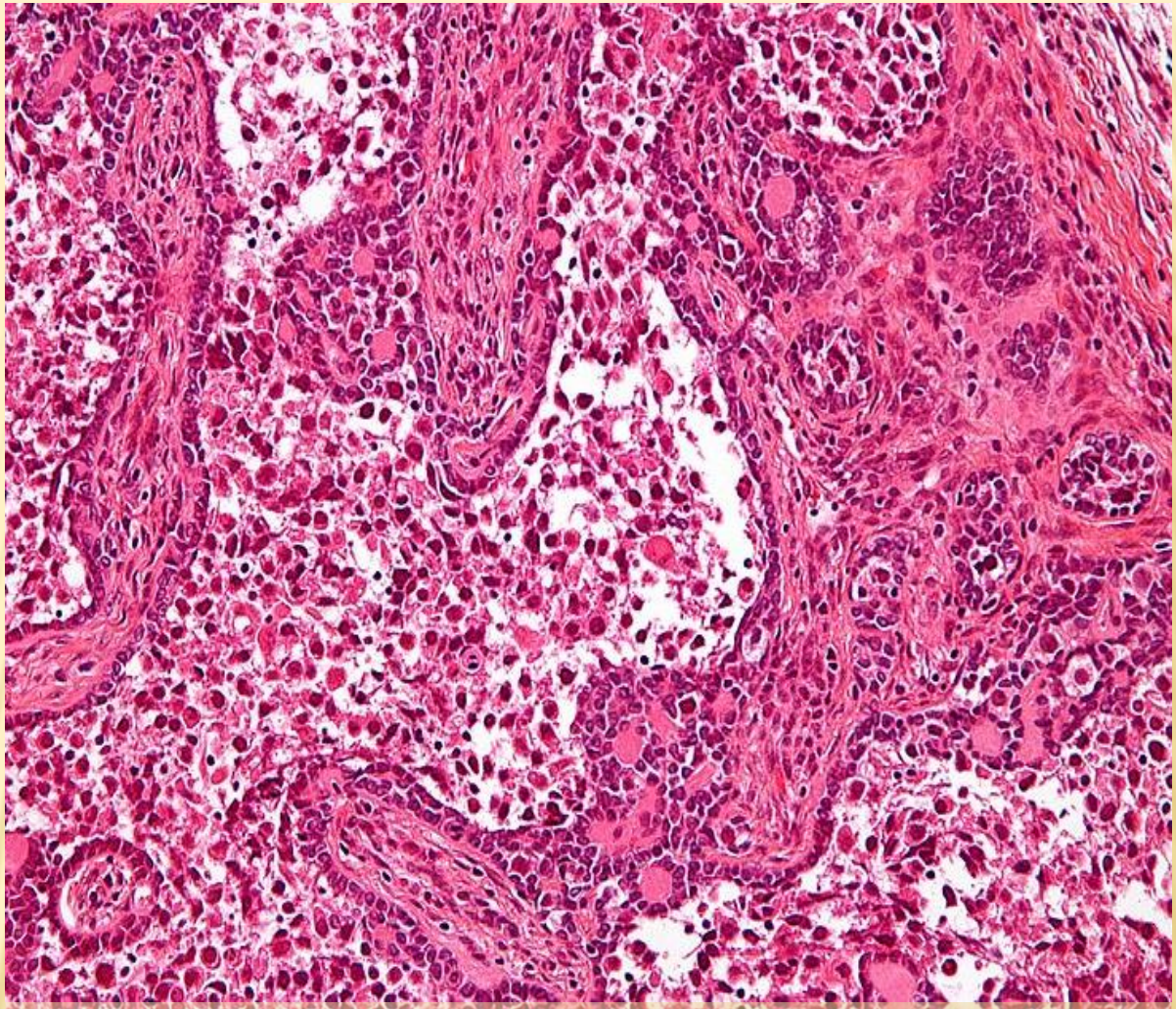
Genotype	Phenotype
45,X	Sexual infantilism (90%) Normal puberty and menses (10%)
45,X mosaic (without Y) (46,XiXq, 46,XX, 47,XXX, 46,X,del(Xp))	Sexual infantilism (30–58%) Normal puberty and spontaneous menarche (70%) * (Sybert7) Normal puberty and spontaneous menarche (42%); only half (21%) had consistent menses in adulthood (Lippe et al8)
45,X/46,XY mosaic with:	
Bilateral intraabdominal streak gonads	Sexual infantilism
Intraabdominal streak + intraabdominal testis	Clitoromegaly
Intraabdominal streak + scrotal testis	Sexual ambiguity
Bilatral scrotal testes	Normal male with infertility

* Ovarian and menstrual function may be short-lived indicating a high degree of gonadal dysfunction.

VERY IMPORTANT TO ORDER A CELL FREE DNA TEST FOR Y CHROMOSOME

CFD: POSITIVE FOR Y CHROMOSOME

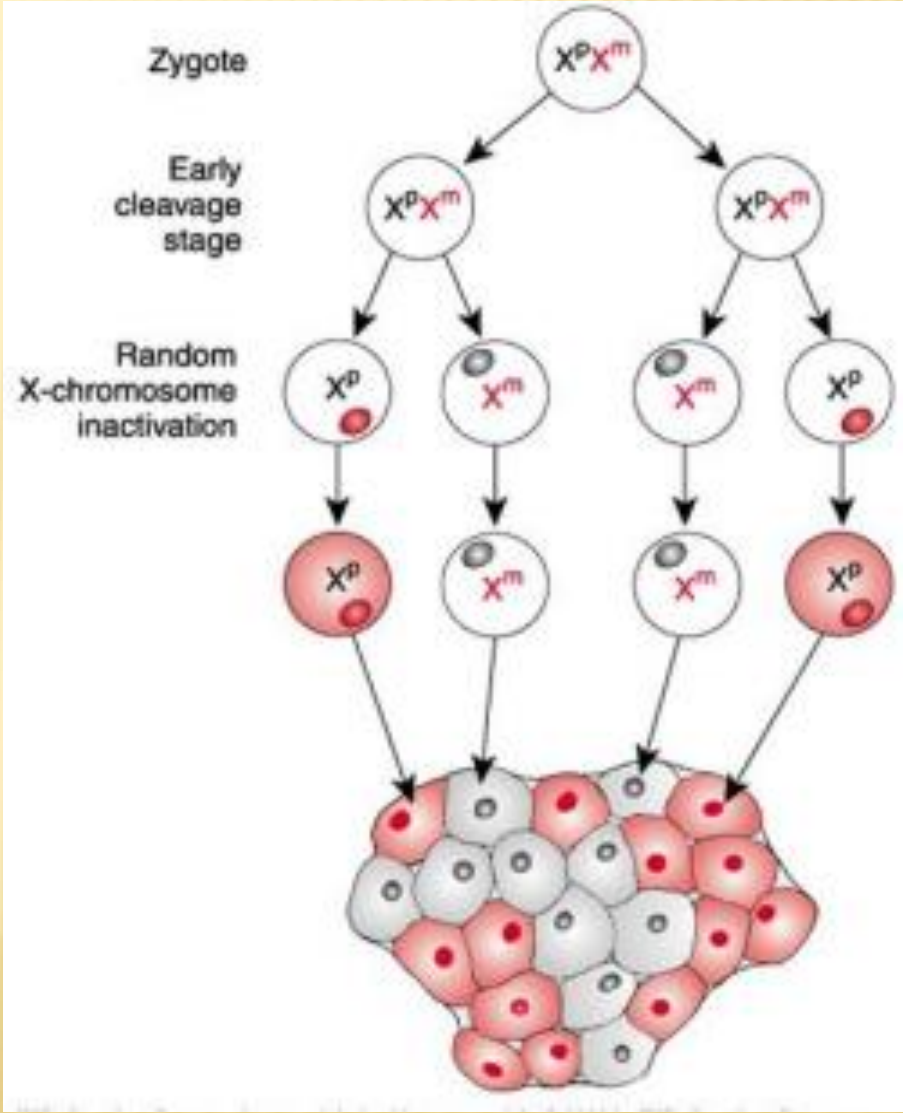
- Sara may have started life as a 46,XY conceptus and lost the Y chromosome in one of the early mitotic divisions.
- DNA study show mosaic state ;45X/46XY
- If any of the cells in her streak gonads retains a Y, these cells can give rise to a malignant gonadoblastoma.
- Therefore it is important to check for the presence of Y-chromosome DNA sequences.
- If any are found, then gonadectomy is usually recommended.



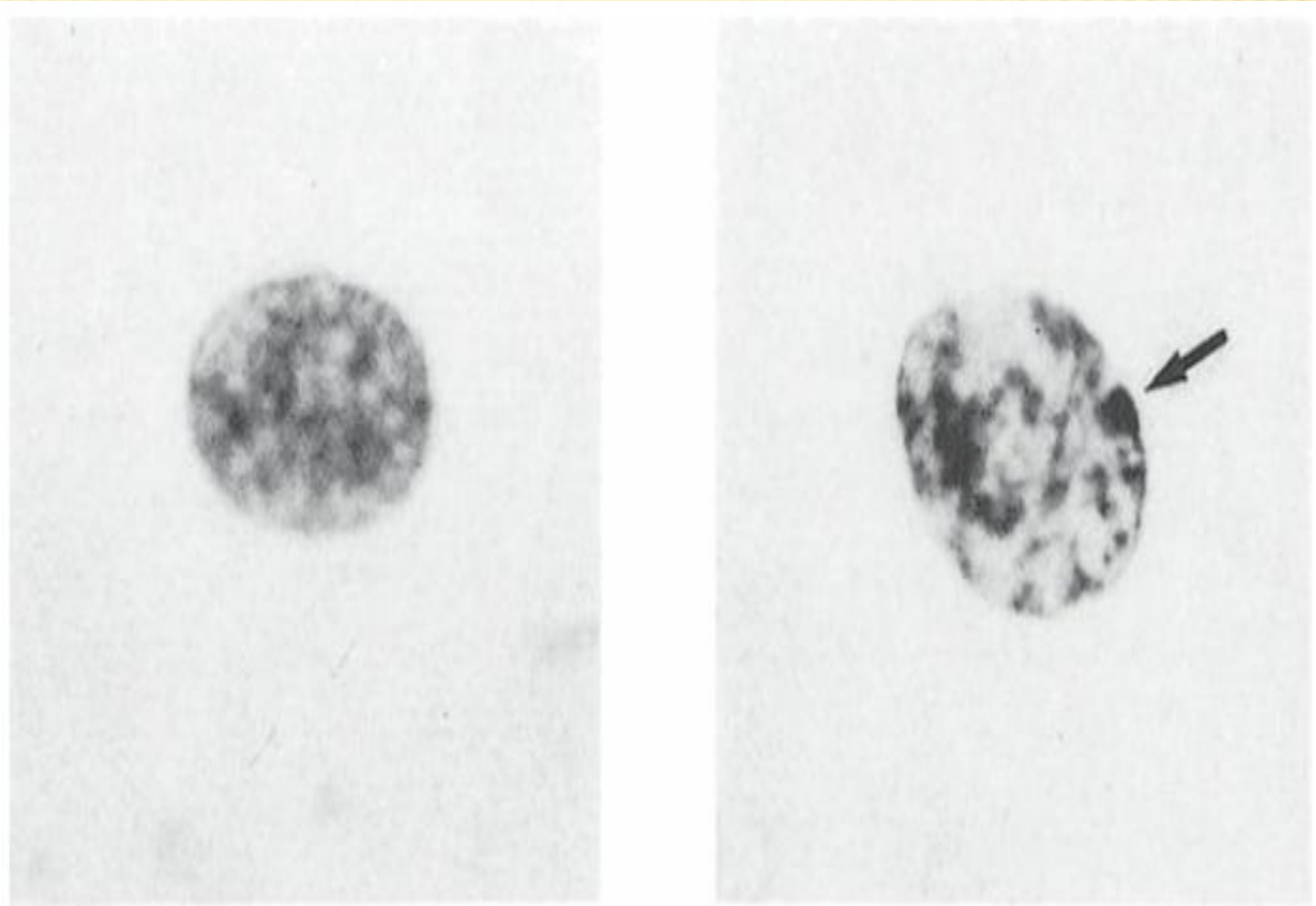
GONADOBLASTOMA

X INACTIVATION PHENOMENON

- Any X chromosomes in excess of one are genetically inactivated.
- Normal females are 46,Xx, normal males are 46,XY; Turner females are 45,X



(X) INACTIVATION ; BARR BODY



X INACTIVATION IS NECESSARY FOR NORMAL DEVELOPMENT IN WOMEN

- Not all genes on the X chromosome are subject to X-inactivation.
- about 15% of X-linked genes escaped inactivation partially or totally, and a further 10% showed differences between different inactive X chromosomes in the degree of inactivation.

MOLECULAR GENETICS OF TURNER

- Some X-linked genes that escape inactivation have counterparts on the Y chromosome, and these will have lower expression levels in Turner women than in normal men or women.

GENOMIC IMPRINTING

- It has been claimed that behavioral problems depend on whether the single X chromosome is of maternal or paternal origin.